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SUPPLEMENT 199 1969

TAPE RECORDINGS OF THE
ELECTROCARDIOGRAM IN
NEWBORN INFANTS

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INTRODUCTION

At birth a haemodynamic revolution occurs in the circulation. A series of integrated events follow each other within a couple of minutes: the aeration of the lungs is accompanied by the inception of functional pulmonary circulation; the placental circulation ceases and the ventricles of the foetal heart, coupled in parallel, are reconnected in series by means of the closure of the foetal circulatory shunts, the foramen ovale and the ductus arteriosus. These perinatal cardio-pulmonary adjustments are the largest of the entire human life. A delay or inco-ordination of this transformation may have serious consequences. The magnitudes of both depolarization and repolarization deflections of the electrocardiogram, are proportional to the myocardial muscle mass, and reflect cardiac cell metabolism. Thus, information about the adaptation of the heart to the haemodynamic changes can be obtained from the electrocardiogram.

In obstetric departments and neonatal wards there is a tendency towards more and more intensive observation and therapy of newborn infants. The important primary functions, respiration and heart action, are to be continuously monitored. It is thus essential for correct diagnosis to know the limits of the normal variation of these functions,

and also features typical of pathological conditions. This presupposes the use of long term recordings in research work.

Continuous electrocardiographic and heart rate recordings without affecting the activities of the subject, are produced in two main ways: 1. using a miniature electrocardiographic transmitter attached to the patient, and a special receiver for detection and reproduction of the signal (radiotelemetric instruments), or 2. employing a small portable electrocardiographic tape recorder connected directly to the patient. A third method, applicable also to these two apparatuses, is to conduct the electrocardiographic signal directly to a computer where the information can be processed automatically but this can scarcely be realized in most hospitals at the present time.

The purposes of the present investigation are, to define a suitable and interference-free electrocardiographic tape recording technique for small infants; to study peculiarities in the signal reproduction of tape recording equipment, and to determine the alteration of the heart rate and the electrocardiographic signal postnatally in full term and premature infants, with long-period recordings beginning on the first day of life.

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CONVENTIONAL ELECTROCARDIOGRAPHY IN NEWBORN INFANTS

Full term newborn infant

Paediatric electrocardiography was started by the investigation of Nicolai & Funaro [61] in which a deep S_t deflection, different from the S wave of adults, was found to be a distinctive electrocardiographic feature of small infants. Thereafter an enormous number of studies have been performed the character of which has followed the evolution of electrocardiographic techniques and of modern views of human haemodynamics. The electrocardiographic peculiarities of childhood have been designated as a function of age. The transformation of these features appears to be rapid in early infancy particularly during the neonatal period. As a result of this, the ECG of the newly born cannot be compared with that recorded days, weeks or months after birth.

Neonatal electrocardiographic findings were described in such publications as Hecht [34] Smith [83] Burgard & Wunnerlich [8] two detailed articles of Nadrai [59 60] that of Battro & Mendy [5] Schaffer et al. [78] Tudbury & Atkinson [92] and Allmurung et al. [2]. In the light of these investigations and the monograph *Electrocardiographic Studies in Nor-*

mal Infants and Children by Ziegler [112] it was possible to define the typical features of the neonatal ECG as follows

- 1 The mean heart rate was 120 to 130 beats per minute, ranging from 90 to 200 beats per minute.

- 2 The neonatal P waves were found higher than those of older children, and the duration of the P wave became longer after the neonatal period. Nadrai showed that the P-R interval was prolonged in newborn infants [60].

- 3 The ventricular depolarization complex indicated right ventricular preponderance, which later in childhood gradually turned into the left ventricular dominance peculiar to adults. A prominent Q wave was often detected in standard leads II and III, and left precordial leads.

4. Inverted T waves were quite common in the precordial electrocardiogram without any evidence of myocardial disease. Also a small S-T deviation up to 0.2 mV was often established in chest leads.

In the investigations published after 1950 contradictory reports concerning neonatal T wave alterations were checked. Both Ziegler [112] and Furman & Halloran [23] divided the neonatal period into smaller segments. In this way it proved possible to clarify ventricular repolarization during the first hours, first days and weeks after

birth. According to these later observations the T wave was at first mostly positive in the right precordial chest leads, later becoming inverted [14, 16, 30, 72, 84, 86, 107]. On the other hand, left precordial T waves were negative immediately after birth and became positive later on. Schaffer et al. noted that the T wave was negative on the right, and positive on the left precordium [76]. Also Furman & Halloran detected inverted T_{V1} in more than 50 per cent of newborn infants; there were no negative left precordial T waves in this series [23]. Sodi Pallares et al. paid attention to the convex S-T segment, and peaked, asymmetric T wave, peculiar to the neonatal right precordial electrocardiogram [84]. Stern & Lind found that the inversion of T_{V1} occurs between the ages of 30 minutes and 6 days [86]. This was confirmed by DePasquale & Burch [17]. Scott & Franklin reported that the T wave inversion in the right chest leads occurred during the first week of life [30]. Halt & Gasul showed that the axis of the T wave initially for 0-5 minutes post partum, pointed to the left, then shifted to the right at the age of 1-6 hours, and then once again to the left in a time of seven days. This variation was suspected to be a sign of transient physiologic left ventricular strain [32].

The comparison of electrocardiographic findings with neonatal haemodynamic observations offered new possibilities for explaining T wave alterations. Dupuis et al. demonstrated that changes of T_{V1} coincided with the disappearance of pulmonary hypertension [19]. Emmanouilides et al. established a correlation between positive right precordial T waves, high P waves and pulmonary hypertension. There

was also a positive correlation between the negative T_{V1} deflections and a neonatal left to-right shunt in ductus arteriosus. R/S ratio in the V6 lead was found to be less than one in cases where the pulmonary arterial pressure was low in relation to the systemic arterial blood pressure [20].

The U deflection was rather rare in the electrocardiogram of newborn infants. Michaëliason found U waves up to 0.3 mV of magnitude in about one third of infants at the age of one week or less [54]. This observation was confirmed by Walsh [107].

The monograph of Wasserburger gave data about normal and abnormal QRS complex morphology in unipolar leads during childhood. This material included a group of 50 infants 0-2 months old, 40 of whom were under 1 week old. Rr and rR patterns were mostly discovered in the right chest leads and qRs pattern, with a tendency to low voltage and clockwise rotation, was a typical finding of left precordial ECG [110].

Interracial differences in neonatal ECG were described by Sutin & Schrire [90]. Right ventricular preponderance was reported as more prominent in white infants than in South-African coloured and Bantu infants.

According to the literature, there seems to be much variation in the values of different conduction phases of neonatal electric cardiac activation. The duration of the P wave ranged from 0.02 to 0.10 s [23, 24, 54, 69, 102, 106, 112]. The P-R time was 0.06-0.14 s [23, 60, 72, 102, 106, 112] and the QRS interval 0.04-0.08 s [23, 54, 60, 69, 72, 103, 112]. The measurements of these intervals were generally performed in standard lead II. DePasquale & Burch stated that the duration of P

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deflection was constant in the neonatal period [17]. The results of Ziegler [112], Walsh [102] and Jagielski et al. [39] indicated a shortening of the P wave duration after birth. The heart rate had no effect on the duration of atrial depolarization. Generally shorter P-R intervals appear with higher heart rates, but in newborn infants this phenomenon is less marked [3]. Kessel found that the P-R interval was longest 3-5 hours after birth regardless of heart rate [42]. Also in the series of Michaëlsson, the maximal P-R intervals were noted during the first day of life [54]. A gradual decrease of the P-R interval in the neonatal period was a common finding [17, 39, 12, 106]. The minimum interval was reached in 1-7 days [112].

The duration of the ventricular depolarization complex was minimal during the first 4 weeks of life [23, 112]. DePasquale & Burch [17], Walsh [103] and Jagielski et al. [39] established the decrease of the QRS duration in their newborn materials. The materials of Nadrai [60], Ziegler [112], Michaëlsson [54], DePasquale & Burch [17], Walsh [103] and Jagielski et al. [39] indicated a transitory prolongation of the Q-T interval after birth. Walsh demonstrated that the prolongation of the Q-T interval was mainly due to the prolongation of the duration of the S-T segment [103].

An extreme variation exists between different investigations in respect to the frequency of cardiac rhythm and conduction disturbances during the neonatal period. A common characteristic of all these disturbances, however, is that they are asymptomatic. Some investigators have not mentioned any arrhythmias, although quite large materials have been examined. The possi-

bility of the appearance of a sudden arrhythmia in a short recording is rather small and, on the other hand, mild sinus arrhythmias would not be classified as true arrhythmias by all authors.

The most frequent arrhythmia in newborn infants seems to be the sinus arrhythmia [16, 23, 30, 54, 59, 60, 68, 92, 112]. The highest incidence of respiratory arrhythmias (42 %) was reported by Nadrai [59]. There are regularly more sinus arrhythmias to be detected in association with lower heart rates [112]. In most investigations there were only sporadic cases of extrasystole [19, 23, 54, 59, 60, 72, 53, 92], although authors found premature beats in as much as 30 per cent of their material [8]. Ventricular extrasystoles proved to be more common than supraventricular ones.

Single cases of auricular flutter [112], wandering pacemaker [23, 72, 104], Wolff Parkinson White syndrome [104], nodal rhythm [19], sinus arrest and supraventricular arrhythmias [54] were discovered in newborn materials. Most of the arrhythmias occurred on the second and third day of life [54]. Ziegler described an infant with a grave transitory ventricular conduction disturbance [112]. Both Schaffer et al. [78] and Walsh [104] found one case of right bundle branch block in their materials. There was also one case with a ventricular conduction disturbance in the material of Stern & Lind, which normalized during the observation time [85].

In an impedance pneumographic and electrocardiographic study we found sinus arrhythmia in 60 per cent of the material of 50 newborn infants at ages of up to 10 days. Half of the sinus arrhythmias appeared to be connected

with periodical respiration. Although the recording time was very much longer than in ordinary ECG examination, no other arrhythmias were detected [15].

Heart arrhythmias in childhood was the theme of the monograph of Landtman [45]. No special attention was paid to the neonatal period, but it was mentioned that sinus arrhythmia was found, although less pronounced, in the youngest age groups too. Premature beats, auricular flutter and fibrillation, seldom appeared in infants. Two cases of paroxysmal tachycardia, typically occurring in infancy were detected in the neonatal period. Conduction disturbances were also quite rare, only one newborn infant with a complete A V block being described.

Premature newborn infant

According to the early investigations of Noeggerath [62] Hecht [34] Burgard & Wunnenlich [8] Londe [49] Raiha [67], and Nadrai [39-60] it could be concluded that there is no neonatal electrocardiogram peculiar to premature babies, although some features differ from that of full-term newborn infants.

- low voltage in QRS complex was more common in premature material, especially in the group with a small birth weight,

- P and T waves were also of lower amplitude and could even be lacking,

- the premature generally had higher heart rates,

- less respiratory sinus arrhythmia was found among prematures, but real rhythm irregularities were quite frequent [67].

A contrary result was expressed by

Landtman, where many arrhythmias, though not sinus arrhythmia, were rarely found in premature infants [45]. The reason for this discrepancy may be the longer ECG recording time employed by Raiha [67].

More information about the ECG of the premature newborn infants was obtained using precordial leads [38, 47, 74, 75, 76, 87, 101]. Less prominent right axis deviation was found in premature babies than in full-term material, and deep Q waves were common in the left precordial leads. The right precordial T waves appeared to be often negative during the first day of life, which was believed to be a sign of a less marked right ventricular strain than in infants delivered at term. It was suggested by Stoermer that the persistence of positive right precordial T waves indicated abnormal right ventricular hypertrophy [87]. A shift of the negative T wave to the left was a common finding in the series of Thoen [91] Stoermer [87] and Salmi et al. [76]. The left precordial T waves were mostly positive during the first day the same was the case after the second day of life. Thus the behaviour of neonatal T deflections in the left precordial ECG in premature infants resembled that of full-term babies. The P R interval was a little shorter in the premature compared with the values of the full-term neonates, but also prolonged atrio-ventricular conduction was to be detected [74, 75, 91]. The prematures had QRS intervals of the same, or smaller magnitude as the full-term infants [75 III 91].

A profound longitudinal study concerning the evolution of the ECG of premature infants during the first year of life was published by Walsh [105]. According to this work the variation

of heart rate was 100–200/min. The mean heart rate was higher than in full term infants. One case with an abnormal bradycardia of 65 beats per minute was mentioned. Premature babies with a birth weight less than 1500 g tended to have faster heart rates, especially at the age of one to three months. Arrhythmias were quite uncommon in this series. The P wave duration, P R interval and QRS interval increased during the first year of life. The Q-T index had a minimum at one to three months. The right precordial P waves were often peaked or diphasic during the first week of life. This phenomenon had been observed earlier and was suspected to represent a sign of right atrial overload [76 91 101 111] 75 % of the material had a right axis deviation and 6 % had a left axis deviation at birth [105] T deflections were well defined but low in the chest leads, while the observations concerning the direction of T waves were in agreement with earlier investigations. U waves were discovered in about one third of the material at some time during the period observed. They were mostly found in the right precordial ECG.

Peaked P waves and a low QRS voltage were also reported by Fonseca Costa et al. [22]. These authors found a relationship between the greater occurrence of Q_{rs} , negative right precordial T waves, and lower birth weight. This was considered to be a sign of a greater degree of immaturity. The higher P waves, shorter intervals of cardiac activation, and lower voltage of the ECG of premature infants were confirmed by Berlinerblau [7] and it could be concluded that no clear electrocardiographic signs typical of premature infants could be defined.

CONTINUOUS ELECTROGARDIOGRAPHY

Conventional electrocardiographs have some disadvantages for special purposes. Long term recordings are uncomfortable for the subject, because he is connected to the instrument and thus unable to perform normal activities. On the other hand these cardiac changes during every-day work are the most important criteria for the diagnosis and the degree of invalidity of a specific heart disease. Another problem is the adequate analysis of a long period segment of electrocardiogram consisting of thousands of signals with almost equal configuration. The length of a roll of a conventional electrocardiograph paper is also a limit for recordings lasting hours or days.

All the problems mentioned above were resolved technically by a small portable electrocardiographic tape recorder (Electrocardiocorder) and the rapid analysing equipment (AVSEP Audio-Visual Superimposed Electrocardiographic Presentation) of Holter in 1961 [36]. These instruments, manufactured commercially by Avionics Research Products Corporation, Los Angeles, California, will be described more thoroughly in section 1 of this investigation.

Observations concerning the clinical use of Holter's tape recording system were published by Gilson et al. [27]. Attention was paid to reducing the inaccuracy of the recording by improving recording technique. Comparisons were made between the electrocardiographic configuration in unipolar and bipolar chest leads, and also between the fidelity characteristics of a conventional electrocardiograph and those of Holter's instruments. It was concluded

that differing electrode placements produced very similar patterns in both chest leads studied, and thus the bipolar lead CSR-C3 was accepted for continuous recording. The oscilloscopic presentation in AVSEP differed from the pattern produced with the conventional machine. These differences included deeper III waves, slight deviations of S-T segment and deformations of T wave (so-called pre-T notch and post T dip). Basic electrocardiographic patterns of healthy adults were presented. The P wave and QRS complex were found to be quite stable, whereas the S-T T segment showed both dynamic and individual variations. Some features of the most common arrhythmias were presented, and difficulties in their identification were discussed. Stress was also laid on the importance of experience in excluding artifacts produced by the system itself.

Both Norland & Semler [63] and Corday et al. [13] used Holter's instruments to examine a large number of patients, mainly adults, among whom they picked up case reports concerning evanescent cardiac arrhythmias and stenocardiac attacks. Descriptions of the use of the tape recording method including case reports were published also by Arstila et al. [4], Roskamm et al. [71], Matsdorff & Schmidt [31] and Shumak & Brown [81]. Gilaon et al. [28] described 4 cases with unusual QRS alterations among a material of 400 recordings. Gilaon [25] published a longitudinal study of AVSEP-patterns recorded in adult men during four years. It was found that a similar basic pattern was recorded every year in 81 per cent of the cases. Alterations were detected mostly in repolarization deflections. Arrhythmias were surprisingly rare. Sanders & Marti [77] reported observa-

tions of the use of electrocardiographing at high altitude.

The advantages and limitations of Holter's method were discussed on the basis of carefully standardized recordings performed in a large group of active adult men [25]. The characteristics of several Electrocardiographs of different type series were compared. The speed constancy and cumulative timing error of the new Model 350 C series were found to be better than those of the older Model 350 C. Also a small time non-linearity in the scanner time-base was detected. A marked decay at the end of a test square wave was observed both in the scanner and charter outputs. The final ECG writer of the charter was not responsible for this phenomenon. The over-all frequency response was confirmed to be practically equal with that specified by the manufacturer. These results indicated that some distortion, especially in the low-frequency components, i.e. S-T-T region, of the ECG is to be expected. This fact was also confirmed by studying the configuration of an ECG test signal. There were often difficulties in identifying S-T deviations and arrhythmias with the scanning technique. It was concluded that the interpretation of changes particularly affected by the electronic peculiarities of the instruments, e.g. S-T deviations and T wave abnormalities, can lead to false results, when the limitations of the method are not understood. For a more accurate analysis of recordings a photographic write-out of R-R intervals with real-time scanning, and a careful examination of all potential segments of abnormality was recommended.

Short case reports of arrhythmias, e.g. conversion of paroxysmal tachycardias

to sinus rhythm, A V blocks of different degrees, and ectopic pacemakers in childhood, studied with Holter's apparatus, were published by Morgan et al. [56] and Välimäki [96]. The former investigation included an example of processing the tape through a computer to obtain a histogram of R—R intervals.

CONTINUOUS ELECTROCARDIOGRAPHY IN NEWBORN INFANTS

In 1965 Morgan and Guntheroth published data obtained from 50 newborn infants at the age of one hour to 7 days by means of Holter's apparatus [57]. Standard lead I was used and recordings were taken for 3 1/2 to 5 hours. Primary attention was directed to the cardiac rhythm. Sinus arrhythmia was observed in all infants. The heart rate varied from 70 to 180 per minute. Occasional premature beats were found in a few infants. One case of incomplete atrioventricular block was also mentioned. Thus quite a nor-

mal cardiac mechanism was usually found in full term babies.

The case was otherwise with premature newborn infants, according to the earlier report of Morgan et al. [55]. The series consisted of 20 infants at ages from 11 hours to 29 days. A marked sinus bradycardia was observed in 8 cases and 5 additional infants had sinus bradycardia with nodal escape. One infant had a first degree A V block. Sinus bradycardia was more common in the lower birth weight groups. The effect of digitalization and the vegetative tonus of premature infants were discussed on the basis of these results.

Our team also introduced two case reports of newborn babies, one with vegetative T wave changes after crying and the other with 2:1 A V block, which was transformed first to sinus rhythm, then to a bizarre ventricular conduction pattern, and later once again to sinus rhythm with S—T deviation [4]. Preliminary reports of the present investigation were published in abstract form [95-97].

PRESENT INVESTIGATION

SECTION I DEVELOPMENT OF METHODOLOGY

THE EQUIPMENT OF HOLTER-AVIONICS

The frequency components of human electrocardiographic signals include too low frequencies to be directly utilized in electronic apparatuses. Thus higher frequency carrier wave, modified (frequency modulated) by the cardiogenic signal, is employed in units that allow long segments of ECG to be recorded on a magnetic tape. For this procedure, large, complicated, and expensive devices are required.

Full freedom in transportability of the recorder and relative simplicity of the analyzer unit were gained, at the same time avoiding the frequency modulation, in the electrocardiographic tape recording method introduced by Holter [36]. The apparatus of this method consists of a small, battery powered recorder (Electrocardiocoder[®]), a rapid analyzer (Electrocardioscanner[®]), and writer unit (Electrocardiocharter TM).

Electrocardiocoder

Electrocardiocoder Model 150 is a miniature twochannel recorder weighing 1330 g. designed to be carried by the subject. The tape speed is exceptionally slow only 0.21 cm. The frequency response of the machine is 0.1—100 cps. The ECG signal is simultaneously recorded on two tracks of the tape by the two channels of the device. One is the actual ECG pattern channel by which the ECG is amplified, and, mixed with bias alternating current, recorded on the tape in the pattern recording head. The other is a trigger channel by which the ECG pulse is transformed into sharp trigger pulse. The trigger

head is located at some distance from the pattern head, which enables slightly earlier recording of the trigger signal on the tape. The purpose of this arrangement is that the trigger signal will trigger the sweep of the pattern display of the Electrocardioscanner and the QRS complex of the synchronous pattern recording will be placed in the middle of the sweep. Small reels of magnetic tape provide a recording of 5 to 18 hours, depending on the thickness of the tape. The capacity of the power supply a small nickelcadmium battery restricts the continuous recording time to 10 hours. The original electrodes and cords are for bipolar leads. A marking and calibration deflection of 1 mV may be recorded on the tape by pushing a calibration button in the operating panel of the Electrocardiocoder. A repetitive one-millivolt pulse, with frequency of 1 cps, can be obtained by means of the One-Millivolt Calibrator (Avionics) in order to calibrate the scanner unit.

Electrocardioscanner

The recording is analyzed at a 60 times accelerated tape speed in the Electrocardioscanner Model 150. Thus a band width of 6—6000 cps is reached, and the ECG potentials can be reproduced without frequency modulation. The accelerated play back technique also enables the rapid analysis of a long recording. The ECG pattern signal is applied through an amplifier to the ECG-pattern oscilloscope (AVSEP[®]) of the scanner. The trigger signal is utilized to adjust the length of the sweep of the oscilloscope equal with the R—R interval. This produces a superimposed presentation of successive ECG complexes on the screen.

Thus sudden changes in the ECG are easily detected as a movielike alteration of the PQRS configuration.

A saw tooth voltage proportioned to the recorded R-R intervals, is fed to the other oscilloscope (Arrhythmigraph) of the scanner unit to indicate the variation of the heart rate, which is also to be heard as a steady growl through a loud speaker. This AVSEP technique enables the examiner to concentrate on following the ECG pattern on the screen, while the heart rate can be heard at the same time. Phenomena recorded on the tape can be timed by comparing the diary notes of the Electrocardiometer examination and the time reading in a small clock of the scanner which is mechanically turned by the tape. Both oscilloscopes are to be calibrated independently with the one-millivolt rectangular pulse. This pulse is a reference for both voltage and timebase calibration.

Electrocardiocharter

If electrocardiographic abnormalities are detected during the play back procedure in the scanner these can be written out by means of the third unit, Electrocardiocharter Model 550. The original recording is placed on the operating deck of the machine where the tape speed is once again the original 0.31 cm/s. The movement of the recording can be followed with a real time clock similar to that of the scanner. Because of the slow tape speed, the gap of the reproducing head of the charter must be unusually wide to detect the slowly changing magnetic field. The signal is amplified and fed to the input of an oscillograph (Burdick EK III Electrocardiograph) to be printed on a conventional ECG paper.

The operation demands (small size, portability signal reproduction of good quality simple construction) of the Electrocardiometer AVSEP instruments have led to some technical compromises in the manufacturing of these devices. The stability of the baseline is achieved by restricting the low frequency response, which leads to some insufficiency in repeating some essential frequency components of the ECG. It has been stressed that findings obtained with

this method are not comparable to those of conventional electrocardiography [27-35]. Although a considerable non-linearity of the frequency response already exists in the recorder stage, additional distortion is evidently produced by the charter procedure. To avoid these distortions an additional method has been developed for printing the recorded tape information on ECG paper.

MV 1 METHOD

This method was designed for a cardiological laboratory in which there is regular ECG equipment, e.g. electrocardiographs and oscilloscopes available, and thus only two additional components, a tape recorder of high quality and a special FM-modulator-demodulator MV 1 are needed. This last has been developed and tested in the electronic laboratory of Lääketukku Oy Helsinki, Finland, and in the Cardiorespiratory Research Unit of the University of Turku. The MV 1 unit itself was constructed by an engineer T. Ahman (Lääketukku Oy). Preliminary reports concerning this method have been published previously [80-113].

According to this method, the original Electrocardiometer recording is analysed in the Electrocardioscanner and during the play back procedure the ECG signal is taken from the ECG output of the scanner to the MV 1 unit. In this unit the signal is frequency modulated and amplified, and then transferred for a re-recording to a regular high fidelity tape recorder. For this purpose we have used an Akai M-8 tape recorder (Akai Electric Co. Ltd., Tokyo), which has the frequency response of 30-25 000 cps. The tape speed of the re-recording is 38.1 cm/s. After the diagnostic portion of the original recording has been re-recorded, the re-recording is played at the tape speed of 4.75 cm/s and the signal is fed back to the MV 1 where it is amplified and demodulated and transferred to a conventional electrocardiograph (Mingograph 24, Elema, Stockholm) to be printed on paper. The whole of this procedure is essential, because normal oscillographs are not able to write all the fre-

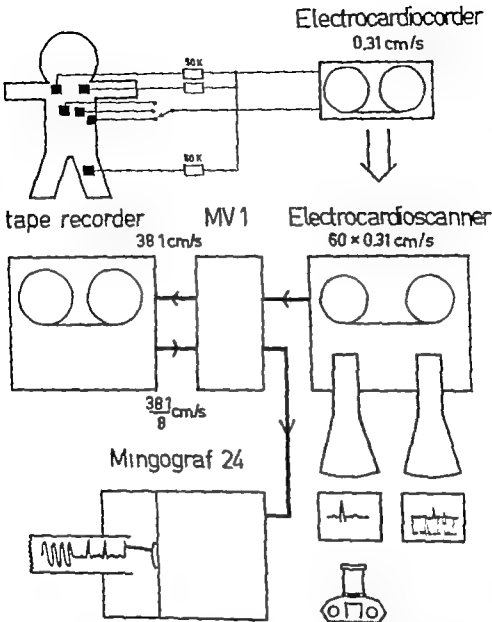


Fig 1 Block diagram of the tape recording and analyzing procedures of ECG with Electrocardiometer and Electrocardioscanner—MV 1—Akai M-8 tape recorder—Mingograf 24 chain.

frequencies of 8–40 000 cps produced by the Electrocardioscanner. As the tape speed of re-recording is reduced to 1/3, a frequency range of 0.75–730 cps is reached. Most rapid oscillographs are able to repeat these frequencies without noteworthy non-linearity. The frequency modulation ensues

better signal reproduction, in fact there are no restrictions with regard to the representation of lower frequencies. An additional oscilloscope is connected to the DC-amplifier of the Mingograf. Thus the ECG pattern of the re-recording is visualized, and the heart rate is to be heard in

the loudspeaker of the Akai tape recorder. Once again an audio-visual presentation is utilised, and this facilitates the detection of momentary alterations of the recorded ECG. For this oscilloscopic display the Atlas 46 A oscilloscope (Atlas Werke A. G. Bremen) has been used.

The block diagram of the electrocardiographing and analyzing procedures is presented in Fig. 1. The recordings of one-millivolt rectangular calibration pulse made with Mingograph 24 and the Electrocardiograph recorder the latter recording written out by means of the Electrocardiocharter and the MV 1 link, are compared in Fig. 2. We have tested the responses of both the scanner unit and the MV 1 link, by making an Electrocardiograph recording with a sine wave pulse generator. The voltage losses detected in the middle of the frequency range of the scanner ECG output being compensated in the construction of MV 1 amplifier.

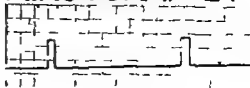
In practice the Electrocardiocharter is troublesome to use, because the original recording must be removed from the deck of the scanner to that of the charter and the interesting point of the recording can thus be lost. The detecting of such a point can be difficult without an oscilloscope control, and involves the expense of much time and ECG paper. In the MV 1 system the final signal can be continuously followed with an oscilloscope and a loudspeaker and only the essential segments need to be printed on paper. The original recording can stay on the scanner deck all the time. These practical difficulties have been partially eliminated in the Composite Electrocardioscanner Model 651 of Avionics, which includes both the scanner and the charter units.

ADJUSTMENTS OF THE APPARATURE FOR THE PRESENT STUDY

Recording

The AVSEP scanner analysis presumes an undisturbed tape recording of the ECG signal. Three major dis-

MINGOGRAPH 24



ECCHARTER



MV-1



ECSCANNER



Fig. 2. Mingograph 24, Electrocardiocharter MV 1 and Electrocardioscanner reproductions of the 1 mV/1 cps calibration pulse of One-Millivolt Calibrator

turbing factors must be eliminated 1) the alternating current noise, 2) the muscle potentials and 3) the wandering of the base line. These factors become particularly important when we have an unco-operative subject like a newborn infant, when we must continue our

recording for hours or days, mostly without oscilloscope control, and when we should like to get electrocardiographic information even during irritation, crying, and movements.

In the present investigation, the occurrence of the local alternating currents in the rooms of hospital wards was determined by utilizing a special antenna loop connected to an electrocardiograph. The place with a minimal inducting alternating current was chosen for recording. A Faraday cage was placed on the bed or incubator of the infant. The connecting wires, of minimal length, were supplied with a metal mantle outside the Faraday cage. The cage, bed, mantle and the case of the recorder were earthed with a single wire. Earthing of the patient was not needed.

Muscle potentials are not a very grave problem, because they are to be seen as small irregular vanishing serrations of the base line during the scanner analysis. The only way to avoid them completely is to place the electrodes far from muscles, and this is sometimes impossible. In this study the electrodes of the central terminal were placed on the subclavicular areas and on the proximal left thigh, an arrangement which also reduced the base line shift. Although this proximal central terminal placement causes a minor reduction of the QRS voltage, this difference is not statistically significant [9].

The proper attachment of the electrodes is essential for minimizing the base line movement, and producing an electrode-skin resistance suitably low for equipment applied. Various standard electrodes and electrode jellies were tried. Finally our own miniature electrodes were constructed, which consisted

of a 1.2×1.2 cm brass net screen connected to the wire by means of a snap fastener. Since the wire had to be exceedingly flexible, it was made of a bearing aid wire in which the conducting metal tape was wrapped around a cotton. The best electrode jelly proved to be Trucon Electrode Paste (Electrodyne, Westwood, Massachusetts). The skin was cleaned with alcohol solution, rubbed until a mild erythema appeared, and the electrode provided with jelly was attached to it with 3M No 1525 Blendederm Tape. Both the jelly and the adhesive tape were well tolerated during a period of 20–30 hours.

Three chest leads, V1, V3 and V5 were recorded successively. These leads were chosen not only because of the high signal-to-noise ratio but also because there is a lot of information about results obtained with chest leads by conventional electrocardiography. This enables conclusions concerning the position of the cardiac electric axis to be drawn from results recorded with these three leads, and finally because the lead system is not too difficult to attach quickly. Resistors of 50 k Ω were connected in the classical manner to the central terminal. A lead selector constructed in our laboratory made the changing of leads possible.

The Electrocardiocorder Model 350 A was used for recording. The original battery of Avionics was replaced by a larger NiFe-accumulator which was connected to the recorder with an earthed wire and an extra plug in jack. This provided power enough for recordings of more than 100 hours without charging. Permatone TX-S-8 magnetic tape was used for registration, the small reels suitable for the recorder being sufficient for 14-hour recordings.

Analysing procedures

The recordings obtained were scrutinised with the Electrocardioscanner Model 450. The AVSEP display of the machine was calibrated by means of 1 mV/1 cps and 1 mV/2 cps calibration pulse recordings, adjusting 1 mV equal to 10 mm and 0.5 s equal to 50 mm on the screen. The higher heart rate scale was utilised on the Arrhythmia graph, which was calibrated according to the 1 mV/1 cps recording.

The ECG configuration was examined directly by measuring the time and voltage quantities on the screen and when necessary the pattern was photographed with an Exa camera (Ihagee, Dresden) on Kodak Tri X film with a close-up time of 1/25 s. The comparison of the values obtained directly and those measured on the exposures showed that sufficient accuracy was achieved by measuring the quantities directly. 0.5 mm was the minimum unit in these measurements.

Suddenly appearing electrocardiographic alterations (e.g. rhythm irregularities, S-T and T alterations) were photographed on the AVSEP oscilloscope. This is not very often elucidating because a large group of electrocardiographic complexes are superimposed on the AVSEP screen during the rapid play back. Therefore the interesting portions of the recording were written out on paper mainly by means of the MV 1 method. For calibration and comparison, the 1 mV/1 cps pulse and the beginning pattern of each recording were registered on paper by the MV 1 technique when the scanner analysis was started. The occurrence of sudden rapid phenomena was carefully timed by the aid of the clock mechanism and the diary.

The Electrocardiocharter was not used regularly in this study for printing the recorded ECG on paper. To secure as much information as possible from the presentation of the recorded ECG most of the sudden irregularities were also written out using either the Electrocardiocharter 550 of the Cardiologic Laboratory of the Mellahti Clinics of the University Central Hospital of Helsinki, Finland, or the new Composite Electrocardioscanner 651 of our own clinic. The results obtained with different analysing techniques are somewhat different, and therefore data and comments are presented in the following chapters concerning the peculiarities, advantages, and limitations of the methodology used.

TECHNICAL OBSERVATIONS

Calibration

The commercial equipment is designed mainly for adults, and therefore the rate of the basal calibration pulse, produced by the One-Millivolt Calibrator is 1 cps. This test pulse is of good quality in the conventional recordings as can be seen in Fig. 2, where also the distortion of this pulse in the scanner charter and MV 1 reproductions is demonstrated. The originally rectangular pulse becomes deformed in the scanner so that there is a small spike of 0.1 mV in the rising loop and a droop of similar magnitude in the descending loop. These artifacts are more marked in the newer models of Electrocardioscanner Electrocardiocharter and Composite Electrocardioscanner than in the apparatus mainly employed in this study. On the other hand, some damp-

ing takes place in the MV 1 link, the pulse becoming rounded in the final presentation.

Besides the standard pulse of 1 cps, another higher calibration frequency is useful when heart rates of small infants are studied. In the present investigation the scanner unit was also calibrated by means of a tape recording of a pulse with frequency of 2 cps, which gives a rate of 120/min, a typical heart rate of newborn infants.

It is impractical to record the calibration pulse in the middle of a long ECG recording. Thus, in contrast to conventional electrocardiography the voltage response of the whole tape can not be checked. Therefore a defective and nonquantitatively magnetized tape segment can be responsible for sudden voltage drops, towards which a reserved attitude must be taken.

Timing error

The clock of the scanner (and charter), is moved mechanically by the tape which turns a small pulley on the deck of the machine. Thus, the exactness of the clock depends upon the friction between the tape and the pulley. Also the properties of the reels, brakes, capstans, and pinch rollers, both in the recorder and analyser, cause some timing errors. These have been studied by Hinkle et al. [35] and a cumulative timing error of +14 to -8 per cent has been presented for Model A recorders. This error is not a constant one during the course of the recording. Our equipment gave an error up to +12 per cent at the beginning, which diminished to zero to the end of the recording, when Permatone TX-S-8 tape was used. We took off the spin from

the take-up reel axis thus there was friction between the axis and the reel, instead of the axis and the rubber loop of the tape transport mechanism. The traction effect of the take-up reel was diminished, and a better time stability of the tape transport was produced. The timing errors could be corrected by means of a regular marking e.g. lead changing, and exact diary keeping.

Base line error

The base line of the scanner oscilloscope is not a straight one as can be seen in Fig. 2. There is a disturbing sine wave of low amplitude present even in the first amplification stage and this must be kept in mind when analysing S-T and T alterations. This distorted base line may be partially responsible for the pre-T notch, an artifact found in one half of the tape recordings studied by Gilson et al. [27]. It does not disturb the analysis, if the duration of S-T segment is not the subject of measurements. The sine wave of the base line is somewhat amplified in the MV 1 presentation. We have not tried to correct this disturbing factor because it seems to be a construction peculiarity in all the equipment we have used.



Fig. 2. The deformed base line of the AVSEP display of Electrocardioscanner: the 50 cps calibration pulse of the scanner amplified with maximal vertical gain.

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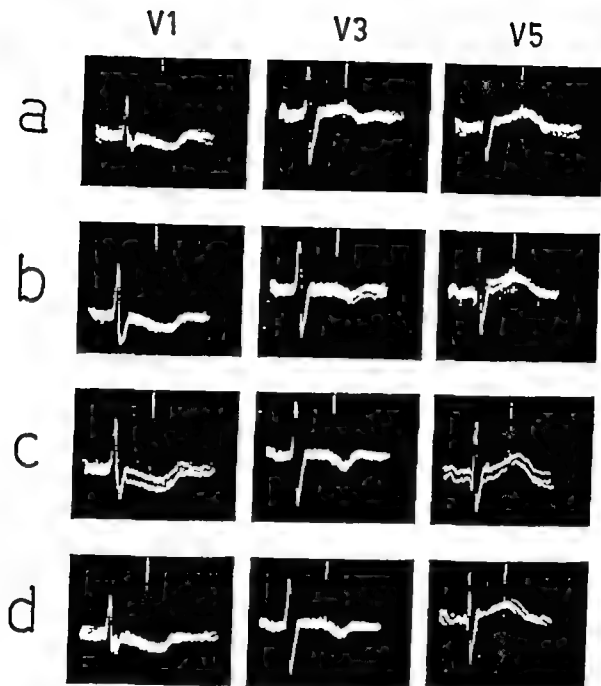


Fig. 4. Effect of posture on ECG tape recording in 6 days old premature male. Electrocardioscanner reproductions of recording performed in a) supine b) right lateral, c) prone and d) left lateral positions.

Effect of postural changes on the ECG

This effect has been noted previously e.g. Holzmänn [37]. Changes resulting from the movement between exploring electrodes and the skin, and/or the heart, are demonstrated in the tape

recordings of Fig. 4. To eliminate these postural artifacts all the recordings were performed in supine position. Because of the long recording time, the infants, especially the premature ones treated in incubators, could change their posture which must be kept in mind when analysing the tapes.

Effect of electrode impedance

A skin-to-electrode impedance of 2—30 k Ω was achieved by the careful skin preparing procedure and electrode attachment described above. The higher values were obtained at the beginning of the recording. This is of the same magnitude described for lead-Nobecutane[®]—gauze electrodes by Gilson & Griffing [26]. The recommendation of the American Heart Association gives an upper limit of 5 k Ω for electrode impedance in directwriting electrocardiographs [11], but the maximal optimal impedance of Holter's device has been mentioned to be 20 k Ω [26].

COMPARISON OF CONVENTIONAL AND TAPE RECORDINGS

Examples of the ECG patterns reproduced by conventional devices and the tape recording devices of Holter were described by Gilson et al. [27]. A conventionally recorded ECG in V5 and CSR—CS leads, was compared with that recorded in CSR—CS lead by Holter's technique. The differences between conventional and tape recording patterns were supposed to be due to the electronic characteristics of these two kinds of recording machines. Exact data, concerning the comparability of the ECG configuration recorded by means of Holter's apparatus with the pattern obtained by conventional technique in the same electrode placement, are not available.

To elucidate this problem, a series of 30 healthy full term infants, 15 boys and 15 girls, were examined at the Obstetric Department of the District Hospital of Loimaa. None of the babies

showed any signs of cardiac anomaly in a careful physical examination. The average birth weight of the material was 3450 g and the average age was 3 1/2 days. Three chest leads, V1 V3 and V5 with a proximally placed central terminal were recorded with the subject sleeping or resting in supine position in the manner described previously in this section (page 18). With the same electrode attachment, recordings were carried out by means of a conventional Mingograph 24 electrocardiograph (Elema, Stockholm) and thereafter with Electrocardiocorder 350 A (Avionics, Los Angeles). The calibration of the conventional ECG was 1 mV equal to 10 mm, that of the tape recording was produced by the One-Milli-volt-Calibrator. The paper speed in the Mingograph was 25 mm/s, the recording time lasting approximately 5 s. Each tape recording included 10 minute segments for each of the three leads.

The durations of P—R interval and QRS, and the amplitudes of P, Q, R, S, S—T deviation, T and U deflections were measured in the conventional recordings. The tapes were analysed in the way explained in analysing procedures (page 20). The data mentioned above were directly measured on the ECG oscilloscope of the scanner during the play-back. The analysis was performed by means of both Electrocardioscanner Model 450 and Composite Electrocardioscanner Model 651. The former was coupled to the MV 1 link, the latter includes the charter unit. The determinations of the electrocardiographic quantities were also made in the MV 1 and charter reproductions.

The data were punched on cards and the information was processed in an IBM 1130 computer. The data of the

Table I. Amplitudes of P, R, S and T waves, and S-T deviations (mV) in 30 conventional and tape recording reproductions of V1, V3, and V5.

P wave (positive deflection)

Reproduction	V1			V3			V5		
	mean	S.D.	range	mean	S.D.	range	mean	S.D.	range
ECScanner 450	0.07	0.04	0.20-0.02	0.09	0.05	0.20-0.03	0.07	0.04	0.20-0.02
Mingograf 24	0.06	0.06	0.30-0.02	0.11	0.06	0.25-0.03	0.06	0.06	0.30-0.03
ECScanner } 651	0.07	0.04	0.20-0.01	0.09	0.05	0.30-0.03	0.07	0.05	0.25-0.02
ECCharter	0.07	0.04	0.20-0.02	0.08	0.04	0.20-0.03	0.06	0.04	0.15-0.02
MV 1	0.06	0.05	0.22-0.02	0.10	0.06	0.25-0.05	0.06	0.04	0.20-0.03

R wave

ECScanner 450	1.12	0.41	1.90-0.60	1.39	0.35	2.00-0.50	0.89	0.37	1.60-0.30
Mingograf 24	1.20	0.45	2.15-0.65	1.70	0.51	2.90-0.70*	1.04	0.47	2.00-0.35
ECScanner } 651	1.06	0.41	1.90-0.50	1.34	0.34	1.90-0.45	0.87	0.36	1.60-0.30
ECCharter	1.04	0.42	1.90-0.50	1.28	0.36	2.00-0.40	0.83	0.38	1.65-0.25
MV 1	0.97	0.36	2.00-0.44	1.18	0.29	1.80-0.44**	0.75	0.32	1.35-0.25

S wave

ECScanner 450	0.57	0.25	1.00-0.10	0.94	0.20	1.50-0.60	0.77	0.20	1.20-0.30
Mingograf 24	0.76	0.54	2.60-0.10*	1.58	0.52	2.90-0.65**	1.19	0.49	2.40-0.20**
ECScanner } 651	0.61	0.28	1.10-0.10	0.96	0.19	1.40-0.60	0.81	0.19	1.50-0.40
ECCharter	0.49	0.23	0.90-0.05	0.88	0.27	1.60-0.50	0.64	0.20	1.00-0.25**
MV 1	0.49	0.25	1.00-0.05	0.83	0.24	1.25-0.45	0.63	0.25	1.16-0.17*

T wave (main or initial deflection)

	-0.11	0.15	0.20	-0.45	-0.05	0.17	0.25	-0.30	0.12	0.11	0.10	-0.30
ECScanner 450	-0.12	0.21	0.48	-0.58	-0.21	0.19	0.25	-0.58	0.14	0.14	0.50	-0.30
Mingograph 24	-0.12	0.17	0.20	-0.45	-0.08	0.14	0.25	-0.50	0.12	0.12	0.30	-0.35
ECScanner	-0.13	0.17	0.20	-0.50	-0.08	0.15	0.20	-0.48	0.11	0.13	0.50	-0.35
ECScanner	-0.13	0.21	0.25	-0.50	-0.12	0.19	0.25	-0.50	0.12	0.15	0.45	-0.35
MV 1	-0.13	0.21	0.25	-0.50	-0.12	0.19	0.25	-0.50	0.12	0.15	0.45	-0.35

Deviation of S-T segment

	-0.62	0.80	0.00	-0.10	-0.008	0.07	0.00	-0.05	0.04	0.05	0.15	0.00
ECScanner 450	-0.05	0.08	0.00	-0.25	-0.05	0.08	0.19	-0.20	0.08	0.08	0.20	-0.05
Mingograph 24	-0.05	0.08	0.00	-0.10	-0.07	0.08	0.08	-0.18*	0.04	0.05	0.20	-0.05
ECScanner	-0.05	0.08	0.00	-0.10	-0.07	0.08	0.08	-0.18*	0.04	0.05	0.20	-0.05
ECScanner	-0.05	0.08	0.00	-0.10	-0.07	0.08	0.08	-0.18*	0.04	0.05	0.20	-0.05
MV 1	-0.05	0.08	0.00	-0.10	-0.07	0.08	0.08	-0.18*	0.04	0.05	0.20	-0.05

Difference almost significant, * significant, ** highly significant.

Electrocardioscanner 450 reproductions were compared with the corresponding values of 1) the conventional Mingograph 24 recordings; 2) the scanner presentations of Composite Electrocardioscanner 651; 3) the chart presentations of the same, and 4) the write out series of MV 1 system. The significance of differences between the series was tested with the t test. If the risk (p) was.

- $p < 0.05$ the difference was called almost significant
 $p < 0.01$ the difference was called significant and
 $p < 0.001$ the difference was called highly significant.

Results

In the comparison of the five different ECG reproductions, the corresponding durations of P wave P-R interval, and QRS interval were found to be equal.

The mean voltages, standard deviations and ranges of P, R, S, and T waves and S-T deviations in the three chest leads, reproduced by the different techniques, are presented in Table 1, where the result of the t test is also given. No significant difference in the P wave reproduction could be demonstrated between the different techniques. The values of the negative components of 9 cases of diphasic P_{r1} are lacking in the table, but the behaviour of this negative part of the deflection proved to be the same as that of the positive one.

No Q waves were found in the V1 lead, and only in two cases was a miniature Q present in the V3 lead. The only information concerning the Q wave could be obtained from the 18 patients with Q_{12} . The mean Q_{12} in the conventional recording was 0.10

(range 0.05—0.50) mV and the corresponding value in the Electrocardioscanner 450 presentation was 0.16 (range 0.00—0.35) mV. Although too small for inferences, the group of Q values revealed no significant difference between the five ECG presentation techniques.

The voltages of the main ventricular depolarization deflections, R and S waves, are generally lower in the tape recordings than in the conventional recordings. The ability to repeat these deflections seems to be equal in both Electrocardioscanner Model 450 and the scanner of Composite Electrocardioscanner 651. Considerable voltage deficits are produced by both printing methods: the charter of Composite Electrocardioscanner 651 and the MV 1 chain. In the case of the R wave, the difference becomes significant between the scanner display and the conventional recording as the deflection reaches the value 1.70 mV in the conventional ECG (the mean voltage of R_{V3} in the table). A significantly unequal reproducibility is also found in the comparison of the repeating characteristics of the scanner and those of the MV 1 equipment at the level 1.39 mV in the scanner presentation (the mean voltage of R_{V3} in the table). The voltage losses of the R wave in the tape recording become more marked as the magnitude of the R wave increases and the most prominent voltage deficit is produced by means of the MV 1 method.

The ability to reproduce the S deflection seems to be even lower than that of the R wave in the tape recording instruments, when compared with the conventional ECG recording technique. Almost significant voltage deficit is detected in the scanner display of S_{V1} and highly significant ones in those of

S_{V3} and S_{V5} . Still more distortion is produced by the writers, although almost significantly by the charter in S_{V3} reproduction, and by the MV 1 system in S_{V3} and S_{V5} reproductions.

The relations of the Electrocardioscanner 450 and the Mingograph 24 presentations of the R and S waves in $V1$, $V3$ and $V5$ leads are given in Fig. 5.

According to the values shown in Table I the ability to reproduce the T wave configuration is statistically equal in all the techniques mentioned above. The table includes only the initial deflections of the diphasic T waves, which appeared 5 times in $V1$, 6 times in $V3$ and 7 times in $V5$. The results concerning the calculations performed in the terminal portions of these diphasic T waves are similar to those presented in Table I. The polarity of the T wave is always the same in corresponding ECG reproductions. The shape of the T deflection is hard to compare without an analog-to-digital converter but in a rough inspection, the write out of the MV 1 chain closely resembles the conventional ECG recording in this series.

At the end of the QRS complex there is often an extra upright deflection in the scanner and charter presentation of the tape recording. It will be called the post-S spike in this investigation. This spike is a peculiarity of the scanner and charter reproductions; it is not found in conventional Mingograph 24 recordings and it does not appear in the recordings written out by means of MV 1 equipment. The incidence and magnitude of the post-S spike are given in Table II. In this material it is most frequent in the $V3$ lead, where the voltages of the R and S waves are the greatest. It is more frequent and higher in the display of the newer scanner than in that of the older model 450. Its

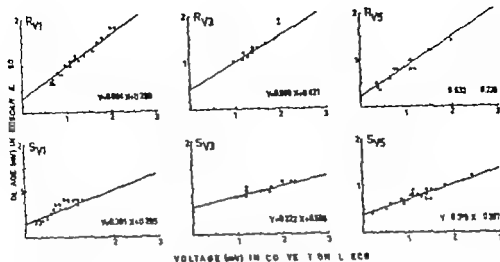


Fig 3 Regressions of R and S wave voltages in V1, V2, and V3 leads calculated from the values of Mingograf 24 recordings and corresponding Electrocardioscanner reproductions of 30 newborn infants.

incidence and magnitude are reduced in the charter procedure.

Depression of the S-T segment was present in the V1 lead in the conventional ECG of 13 infants, in the V2 lead there were 7 cases of S-T depression, and in the V3 lead the S-T deviation was positive in 6 infants and negative in one. The values of S-T deviations in different recordings are presented in Table I. Calculations have been made for the whole population. An almost significantly lower ability to reproduce S-T_{V1} deviation is established

in the scanner display when compared with conventional recording. The MV 1 reproduction best resembles conventional ECG in the S-T and T regions. However the material is small and the S-T deviations are of low voltage. Thus, for reaching conclusions cannot be made according to these results. Conventional and tape recorders of this type do not repeat S-T deviations equally but at least the polarity of the deviation seems to be equal.

The U wave appeared only in V2 and V3 leads. There were 7 infants

Table II The incidence and amplitude of the post-S wave in 24 ECG tape recordings of three chest leads reproduced by Electrocardioscanner 450 and Composite Electrocardioscanner 851.

Electrocardioscanner 450			Composite Electrocardioscanner 851			
			scanner		charter	
Lead	No.	Mean (mV) Range (mV)	No.	Mean (mV) Range (mV)	No.	Mean (mV) Range (mV)
V1	11	0.08 0.02-0.15	18	0.08 0.05-0.20	9	0.08 0.05-0.20
V2	18	0.11 0.03-0.20	27	0.12 0.05-0.30	24	0.10 0.05-0.20
V3	14	0.87 0.05-0.10	30	0.08 0.05-0.18	18	0.08 0.03-0.10

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voltages of the R wave, and particularly the S wave, is found in reproductions of tape recordings when compared with corresponding conventional electrocardiograms. An explanation for these voltage distortions is obviously the restricted frequency response (0.5—100 cps) of the Electrocardiometer. The recommendations of the American Heart Association [9] call for a frequency response of 0.05 — over 500 cps for direct writing electrocardiographs, and that of frequency modulated tape recorders must reach the value of more than 100 cps. According to the recorder-scanner and recorder-chart system frequency response curves of Hinkle et al., the effective frequency range is 0.5—50 cps [35]. Thus a noticeable amount of the electrocardiographic frequency spectrum falls outside the response of this tape recording equipment.

The effect of poor high-frequency response on ECG has been reported to be an increasing attenuation of R and S voltages with decreasing frequency response. The effect on the amplitude of the S deflection is more marked [33]. In ECG writers the mass of the stylus and its friction against the paper further limit the high frequency response below the limits of the circuitry. The results of the present investigation are in agreement with these facts and also with the report of Hinkle et al. [35].

The restriction of low frequency response of the electrocardiograph leads to inaccuracy in repeating wave forms containing lower frequency components, i.e. P-S-T and T (U) deflections, correctly. Thus a progressive attenuation of T wave voltage, and also an increase of S wave amplitude, have been reported to be produced by deteriorating low frequency response [53]. Only a mini-

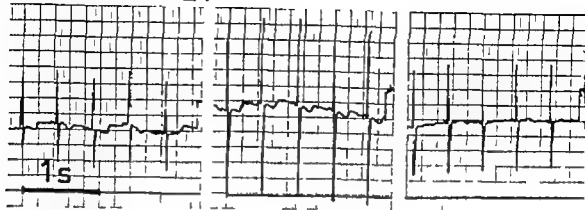
mal and not significant deficit of T wave amplitude was observed in the tape recording presentations of the present study. A minimal S—T segment depression and post T sag have been also considered as artifacts caused by degenerated low frequency cut-off [35, 53]. These findings have already been described in Electrocardiometer-scanner presentations [27]. Significant differences were found in the present investigation between the corresponding recordings in their ability to reproduce S—T deviation, but the S—T depressions did not prove to increase in tape recording reproductions. Because of the inaccuracy of the information available concerning the reproducibility of the S—T segment in the instruments of Holter Avionics, and because of the importance of this segment in the diagnosis of coronary heart diseases, this area calls for more investigation.

Attention has not been paid earlier to the post-S spike, a common finding in the present study. This spike is a small overshoot after a prominent S wave, and deep S waves are not so common in left precordial leads among adults investigated earlier by means of this technique.

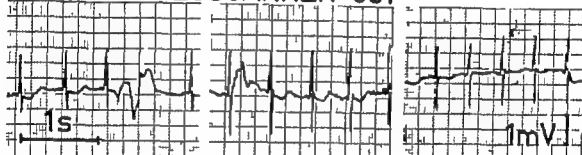
CONCLUSIONS

The Electrocardiometer AVSEP tape recording system of Holter Avionics is a valuable tool when long-term ECG recordings are to be studied. By means of the modified electrode design, and in standardized test conditions, an interference-free recording of unipolar chest leads (V1, V3, and V5) can be obtained. Suddenly appearing altera-

MINGOGRAF 24



COMPOSITE ECSCANNER 651



MV-1



Fig. 6 Comparison of Mingograf 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450 — MV 1 technique.

with U_{13} in some of the 5 reproductions, but only 2 cases with U_{13} in all corresponding reproductions. U_{18} was detected in 2 infants, and it was not repeated correspondingly at all. The maximal amplitude of this deflection was 0.10 mV. The comparison of Mingograf 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450—MV 1 technique is presented in Fig. 6.

Comments

The values obtained by conventional technique, which are presented in Table I are of the same magnitude as those reported by Ziegler [112], Wasserburger [110] and Walsh [104, 107]. The means and maximum values of the R and S waves seem to be a little lower in this material as they were in the earlier study of our group [98].

A considerable attenuation of the

voltages of the R wave, and particularly the S wave, is found in reproductions of tape recordings when compared with corresponding conventional electrocardiograms. An explanation for these voltage distortions is obviously the restricted frequency response (0.5–100 cps) of the Electrocardiometer. The recommendations of the American Heart Association [9] call for a frequency response of 0.05 — over 500 cps for direct writing electrocardiographs, and that of frequency modulated tape recorders must reach the value of more than 100 cps. According to the recorder-scanner and recorder-chart system frequency response curves of Hinkle et al., the effective frequency range is 0.5–50 cps [35]. Thus a noticeable amount of the electrocardiographic frequency spectrum falls outside the response of this tape recording equipment.

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The Electrocardiometer-AVSEP tape recording system of Holter-Avionics is a valuable tool when long-term ECG recordings are to be studied. By means of the modified electrode design, and in standardized test conditions, an interference-free recording of unipolar chest leads (VI, V3, and V5) can be obtained. Suddenly appearing altera-

tions of an ECG pattern are rather easily detected in the play back by means of the Electrocardioscanner and these segments of the tape recording can be transformed into regular paper reproductions with the Electrocardiocharter or the MV 1 equipment described here

The time axis of the devices has been proved to be accurate enough for electrocardiographic research when the timing errors have been eliminated by careful calibration, repeated marking (e.g. changing of leads) and conscientious diary keeping

The electronic properties of the equipment cause some distortions of the voltage axis on the reproductions of the tape recording when compared to a corresponding conventional ECG recording. Because of the limited fre-

quency response of the tape recording instruments the voltage of the deflections with high frequency components, especially that of the S wave, is reproduced significantly attenuated. The same reason is responsible for distortion of the deflections with low frequency components. Thus almost significant differences appear between conventional and tape recording instruments in their ability to repeat S—T deviations. This will be very important in the diagnosis of coronary heart diseases.

The distortions found in the Electrocardioscanner display are often increased in both writing out methods. The unpracticalness of the use of the former Electrocardiocharter Model 550 has been eliminated in the construction of the modern Composite Electrocardioscanner 651

SECTION II LONG TERM ECG TAPE RECORDINGS OF NEWBORN INFANTS

MATERIAL AND METHODS

Material

The material consisted of 90 newborn infants, 80 of whom were born at term. The full term infants were examined at the Municipal Maternity Hospital of Turku, and the premature series in the neonatal wards of the Children's Hospital of the University of Turku in 1964-1968. The birth weight distribution of the material is presented in Table III.

In the full-term group there were 22 boys and 28 girls. They were infants of primiparas in 30 cases and of multiparas in 20 cases. 16 of the mothers

Table III. Birth weight distribution of the material of 80 full-term and 46 premature newborn infants with birth weights of 500-4500 g.

Birth weight	Number of infants
Premature infants	
under 1000 g	1
1000-1500	8
1500-2000	24
2000-2500	15
Full-term infants	
3500-4000 g	4
4000-4500	20
4500-5000	12
5000-5500	11
over 5500	2
Total	80

had received antihypertensive treatment, mainly chlorthalid derivatives, during pregnancy. Of these, 14 had a blood pressure of more than 140/90 before delivery only 2 showed other signs, albeit mild ones, of toxæmia. Abnormalities in the foetal heart sounds during delivery were detected in 2 cases. The delivery was normal except in 2 cases, one infant was born in deflexion attitude one in breech presentation, and one by means of vacuum extraction because of signs of foetal asphyxia. The cord was clamped routinely late, i.e. after cessation of umbilical artery pulsations, but in 10 cases the cord was clamped nearly immediately after the child was born. 47 of the infants had an Apgar score of 8-10. 2 babies had 7 points, and the baby delivered by vacuum extraction had only 5 points. All the infants recovered without any special resuscitative procedures. In a careful physical examination they showed no signs of cardiopulmonary or neurological disorders during the recording procedure or during their later stay at the hospital.

The series of premature infants included 19 boys and 21 girls. 22 of them were children of primiparas, and 8 infants were twins (5 A babies, and one B baby). 9 of the mothers had received antihypertensive drugs during

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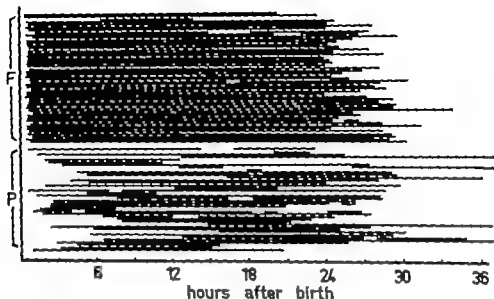


Fig 7 The periods of ECG tape recording in 30 full-term (F) and 40 premature (P) new born infants.

potassium and calcium content were taken from the cord veins, centrifuged immediately and sent to the laboratory for flame photometric (potassium) and titrimetric (calcium) determination. In the full-term group 41 successful determinations of serum potassium and 26 of serum calcium concentration were made. Serum calcium was determined in 4 premature infants using the same methods and the same kind of blood samples, but the potassium content was analysed from microsamples containing capillary blood, in 25 premature infants. All the concentrations represent the electrolyte status at the beginning of the tape recording.

For clinical reasons only the actual acid-base balance was defined according to the micro-Astrup method. Therefore, these determinations were made especially in children who had asphyctic disorders. They were performed only in 18 premature infants.

The analysis of the tape recordings was performed by means of Electro-

cardioscanner Model 450 and the MV 1 method described in section I (page 20).

The initial ECG pattern was photographed on the AVSEP screen in each lead. Otherwise, the different quantities were measured on the screen directly. Thus, every tape was carefully examined, measuring the rather stable voltages of the P, Q, R, S, T and U waves, S-T deviations, and the durations of P wave, P-R, QRS, Q-T and R-R intervals. The heart rate was calculated from the R-R interval on the AVSEP screen, the Arrhythmia-graph was employed for this purpose only in the frequencies below 85/min. The basal ECG configuration, basal heart rate, minimum and maximum heart rates for each hour were estimated. Thus, slowly developing changes of the ECG pattern could be demonstrated. The time corrections were made according to the real time clock and the diary.

The durations of bradycardias below 90/min and tachycardias over 170/min

pregnancy but 14 of them had a blood pressure higher than 140/90 mm Hg measured before or during delivery in the obstetric department. There were 3 mild toxæmias among the mothers, one mother had an actual eclampsia, and one had a grave uræmia. Abnormal foetal heart sounds were found in 2 deliveries. There were 10 exceptional deliveries in this material one infant was born in deflection attitude 4 were pelvic breech deliveries and 5 infants were born by caesarean section. One additional infant was born at home, but she was in quite good condition on arrival at the hospital. No early clamping of the umbilical cord was performed in this series. The Apgar scores one minute after birth were 8-10 in 19 infants 4-7 in 15 infants and 0-3 in 6 infants. Although quite nonhomogenous in its obstetric history the group of premature infants could be paediatrically divided into two quite uniform groups 30 infants who showed no signs of neonatal cardiopulmonary or neurological disorders and 10 infants with a clinical picture of moderate to grave asphyxia lasting throughout the ECG examination 3 of whom died during the electrocardiographic registration. The infants were brought to the neonatal ward mainly because of prematurity at ages ranging from a few minutes to a couple of hours. Therefore the electrocardiographic examination could not be started systematically at birth. On the other hand, these babies stayed a longer time in hospital and they could be clinically examined more thoroughly than the full term group. No infant in either full term or premature group had received digitals or other cardio-active drugs.

Clinical and laboratory methods

In the full term infant group the electrocardiographic tape recording was started as soon as possible after the newborn baby had been removed from delivery room to nursery washed, and placed in bed. The preparation of the skin, the electrode attachment, and the recording technique have been described in section 1 (page 18) Electrocardiocorder Model 350 A was utilized for recording and three chest leads, V1 V3 and V5 were followed successively. At the beginning of the recording an initial registration, using each lead for 10 minutes, was carried out thereafter the lead was changed every one hour. Each recording was started by the author himself, and later the leads were selected according to a routine scheme by the nurses. A diary was kept of these functions and also of all nursing procedures and phenomena observed in the subject (crying, feeding, etc.)

The same registration method was employed when examining the infants belonging to the premature group but the recording was often started later than in the full term group, because many of the premature infants were sent to our neonatal wards from other hospitals. Also there were more often factors (e.g. nursing and resuscitation procedures, respirator treatment) disturbing the ECG recording. The recording times of the full term and premature series are presented in Fig 7.

To control the effects of the main non-circulatory factors affecting the ECG the serum potassium and calcium concentration, rectal temperature and, in the premature group, acid base balance, were determined. In the full term infants, the blood samples for

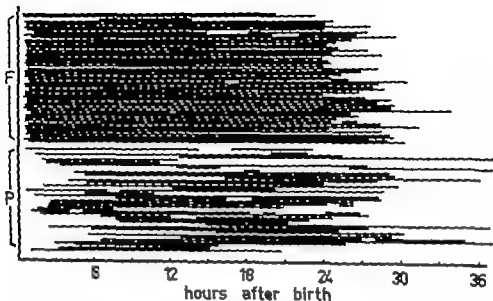


Fig 7 The periods of ECG tape recording in 50 full-term (F) and 40 premature (P) newborn infants.

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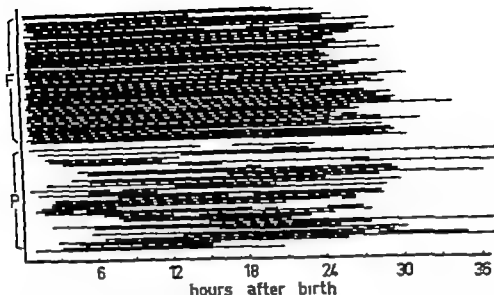


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The duration of observation was 30 min at intervals of 15 min.

were evaluated. Also irregularities in cardiac rhythm and activation were timed, compared with observations of the diary and when necessary analysed in detail by photographing or by writing out the signal on ECG paper in the manner presented in section I (page 20)

Statistical methods

The data thus listed were punched on cards, and the heart rate patterns,

ECG voltage patterns, and changes of various intervals were calculated and plotted in relation to the parameters available by an IBM 1130 computer. Rarely appearing phenomena like sudden electrocardiographic alterations were studied directly without data processing.

The differences between the series were tested by means of the t test. The statistical significance was estimated as mentioned in section I (page 25)

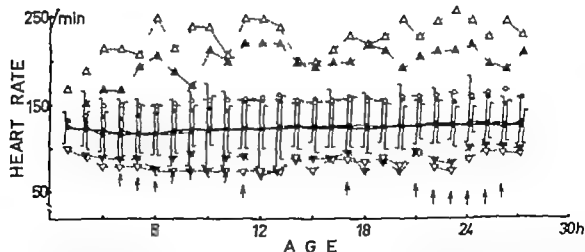


Fig. 8. Heart rate patterns of 50 full term and 30 healthy premature infants. \bigcirc — \bigcirc mean basal heart rate of full term, \bullet — \bullet mean basal heart rate of premature, [range of mean basal heart rate of full term, [range of mean basal heart rate of premature, \bigcirc — \bigcirc mean maximal heart rate of full term, \bullet — \bullet mean maximal heart rate of premature, Δ — Δ peak heart rate values of full term, \blacktriangle — \blacktriangle peak heart rate values of premature, ∇ — ∇ minimum heart rate values of full term, \blacktriangledown — \blacktriangledown minimum heart rate values of premature. Minimum values of 10 asphyctic premature infants differing from those of the healthy premature group are marked with arrows.

HEART RATE PATTERNS

Results

Mean heart rates

The mean basal heart rates, their ranges, and the minimal and maximal, as well as the mean maximum rates for both full-term and healthy premature infants during the observation period are presented in Fig. 8. The curves of premature babies start in the 2nd hour and all the curves have been cut at the 27th hour because of the insufficient number of observations outside this segment. The curves are only for healthy children, although analysis revealed no significant differences between mean heart rate levels of healthy and asphyctic infants.

There are no significant differences between the mean basal heart rates of full-term and premature infants in the whole material. The basal rates reach their minima at the age of 3-6 hours. Thereafter the values gradually increase, exceeding the first hour values of 125/min at the age of 12 hours until the level of 130/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls, between those of children of primiparas and multiparas in the whole material or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive

and non-hypertensive mothers. Fig. 8 shows that the mean basal heart rate is almost equal in the full term and healthy premature infants. The form of the mean heart rate curve of the prematures remains almost equal when the 10 asphyctic cases are included.

The effect of birth weight on the mean basal heart rate was studied by dividing the healthy material into four groups: I birth weight < 2000 g; II 2000-2500 g; III 2500-3500 g; and IV birth weight > 3500 g. The mean heart rate curves of these groups are shown in Fig. 9. There are significant differences between the basal heart rates of small and larger premature babies (groups I and II) from the beginning to the 18th hour of life, and between those of groups III and IV of full term infants up to the age of 24 hours. The period of low basal cardiac rate is most marked in groups II and III. The groups of small premature and large full-term infants have higher basal heart rate values, and the level of basal cardiac frequency remains more constant during the first 24 hours, especially in group I.

There was a low positive correlation (correlation coefficients of 0.37 and 0.22 for full-term and premature infants) between the first basal heart rate value and the corresponding rectal temperature in the whole material. The basal heart rate did not correlate with the serum calcium or potassium content of the material. The values of these parameters are given in Table IV.

When the lower edge of the basal heart rate was considered, it was found that there was a tachycardic group of 14 per cent of the whole material, in which the basal rate was never below 125/min during the observation period.

were evaluated. Also irregularities in cardiac rhythm and activation were timed, compared with observations of the diary and, when necessary analysed in detail by photographing or by writing out the signal on ECG paper in the manner presented in section I (page 20)

Statistical methods

The data thus listed were punched on cards, and the heart rate patterns,

ECG voltage patterns, and changes of various intervals were calculated and plotted in relation to the parameters available by an IBM 1130 computer. Rarely appearing phenomena like sudden electrocardiographic alterations were studied directly without data processing.

The differences between the series were tested by means of the *t* test. The statistical significance was estimated as mentioned in section I (page 25)

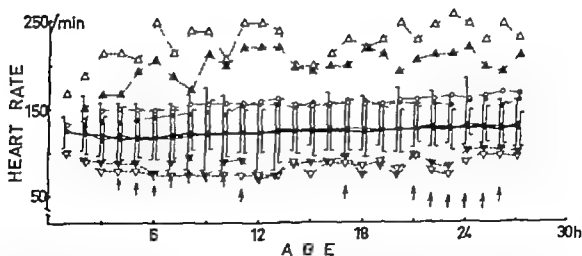


Fig. 8. Heart rate patterns of 50 full term and 30 healthy premature infants. ○—○ mean basal heart rate of full term, ●—● mean basal heart rate of premature,] range of mean basal heart rate of full term, [range of mean basal heart rate of premature, □ mean maximal heart rate of full term, ■ mean maximal heart rate of premature, △ peak heart rate values of full term, ▲ peak heart rate values of premature, ▽ minimum heart rate values of full term, ▼ minimum heart rate values of premature. Minimum values of 10 asphyctic premature infants differing from those of the healthy premature group are marked with arrows.

HEART RATE PATTERNS

Results

Mean heart rates

The mean basal heart rates, their ranges, and the minimal and maximal, as well as the mean maximum rates for both full term and healthy premature infants during the observation period are presented in Fig 3. The curves of premature babies start in the 2nd hour and all the curves have been cut at the 27th hour because of the insufficient number of observations outside this segment. The curves are only for healthy children, although analysis revealed no significant differences between mean heart rate levels of healthy and asphyctic infants.

There are no significant differences between the mean basal heart rates of full term and premature infants in the whole material. The basal rates reach their minima at the age of 3-6 hours. Thereafter the values gradually increase, exceeding the first-hour values 1125/min at the age of 12 hours until the level of 130/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls between those of children of primiparas and multiparas in the whole material, or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive

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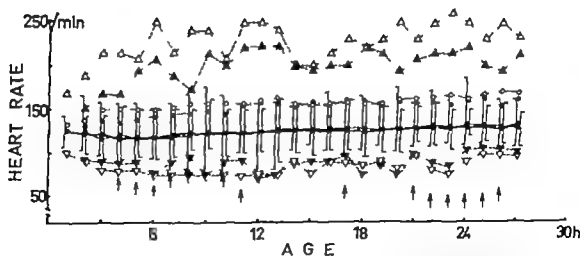


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There are no significant differences between the mean basal heart rates of full-term and premature infants in the whole material. The basal rates reach their minima at the age of 3—8 hours. Thereafter the values gradually increase, exceeding the first-hour values of 125/min at the age of 12 hours until the level of 150/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls between those of children of primiparas and multiparas in the whole material or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive

and non-hypertensive mothers. Fig 4 shows that the mean basal heart rate is almost equal in the full term and healthy premature infants. The form of the mean heart rate curve of the prematures remains almost equal when the 10 asphyctic cases are included.

The effect of birth weight on the mean basal heart rate was studied by dividing the healthy material into four groups: I birth weight < 2000 g II 2000—2500 g III 2500—3500 g and IV birth weight > 3500 g. The mean heart rate curves of these groups are shown in Fig 5. There are significant differences between the basal heart rates of small and larger premature babies (groups I and II) from the beginning to the 18th hour of life, and between those of groups III and IV of full-term infants up to the age of 24 hours. The period of low basal cardiac rate is most marked in groups II and III. The groups of small premature and large full-term infants have higher basal heart rate values, and the level of basal cardiac frequency remains more constant during the first 24 hours, especially in group I.

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When the lower edge of the basal heart rate was considered, it was found that there was a tachycardic group of 14 per cent of the whole material, in which the basal rate was never below 125/min during the observation period.

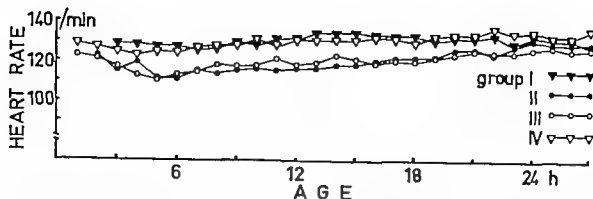


Fig. 9 Mean basal heart rates of infants with birth weight of (I) < 2000 g, (II) 2000—2500 g (III) 2500—3500 g, and (IV) > 3500 g.

In most infants, 70 per cent, the lower limit of the basal cardiac frequency was 100/min, but in the remaining 16 per cent of the material there were periods lasting several hours with a basal rate lower than 100/min. The distribution of the cases with basal heart rates below 125/min was equal in the full term, healthy and asphyctic premature materials. The tachycardic heart rate was present in 8 full term and 7 premature infants. The difference between the incidences of this pattern in the full term and premature groups is highly significant. All the cases with tachycardic basal frequency belonged to the birth weight groups I and IV except one infant weighing 3340 g.

Minimal and maximal heart rates

The lower edge of the cardiac frequency range was just the same in full term and healthy premature babies, as can be seen in Fig. 8. When the means of minimum heart rate values of the healthy in the whole material for each hour were calculated, the curves thus obtained closely resembled the minimum curves of the healthy

cases in Fig. 8. The lowest mean minimum heart rates appeared at the age of 4—8 hours, which corresponds well to the period of lowest mean basal heart rate. No differences could be demonstrated between the minimum heart rates of the healthy premature and full term infants. The lowest heart rate of both healthy premature and full term groups was 85/min. The bradycardic tendency of the asphyctic newborn is shown in Fig. 8 by marking the deviations of the lower edge of the frequency range of the asphyctic premature from that of the normal premature with arrows. These asphyctic bradycardias reached the limit of 50/min, with the rhythm disturbances of dying heart excluded.

Special attention was paid to the occurrence of bradycardias below the value of 80/min. The incidence of cases with heart rate below this value is presented in Table V. The accumulation of these bradycardias in females is statistically almost significant. It can be seen that bradycardias appear in almost every asphyctic premature. The total number of sudden bradycardias was 48 during the recording time of 1248 hours in full term, 23 during 614 hours in healthy premature and 38 during

T b1. IV Rectal temperature, serum potassium, and calcium values at the beginning of recording in 60 full-term and 40 premature infants.

Material	Rectal temperature (°C)			Serum potassium (mEq/l)			Serum calcium (mg/100 ml)		
	No. of cases	mean	range	No. of cases	mean	range	No. of cases	mean	range
Full-term	59	36.5	35.6—37.0	41	5.3	4.0—7.4	28	11.1	9.3—13.1
Premature	40	35.1	33.3—36.9	35	6.6	4.3—8.9	4	10.5	9.5—10.9

120 hours in asphyctic premature infants. The frequency of the brady cardiac phases is nearly the same among the healthy infants, but 10 times higher among the asphyctic infants. The duration of the bradycardias was less than $\frac{1}{2}$ min in $\frac{2}{3}$ of the total number of bradycardias in the full term in $\frac{1}{3}$ of that in the healthy prematures and in $\frac{1}{4}$ of that in the asphyctic premature material. Thus the premature infants, especially asphyctic ones, had a tendency to longer bradycardias. Maximal reversible bradycardia in asphyctic children lasted 35 min. No correlation of bradycardias with external observations of the subject was established, although in asphyctic babies they often occurred during apnoeic attacks. Nor was any relation detected with the age of the baby.

The upper limit of the cardiac frequency range seems to be higher in full-term than in premature infants in Fig. 6. The inclusion of asphyctic cases does not alter the maximum values of the healthy premature. In Fig. 8 there are also the mean maximum heart rate curves, which differ significantly during the first 10 hours. The maximal frequency for full-term babies was 260/min, that of premature ones was 222/min.

The duration and number of tachycardias with a rate over 170/min were estimated. The distribution of cases with one or more tachycardias of this kind between the sexes, and between the full-term and premature groups, is presented in Table V. No differences could be demonstrated between the healthy groups and between the sexes, but between the asphyctic and healthy prematures a highly significant dif

Table V Number of infants with bradycardias of less than 90/min and tachycardias of more than 170/min in ECG tape recordings of 99 newborn infants.

Material	Bradycardias <90	Tachycardias >170
50 full term infants	15 (30.0 %)	40 (80.0 %)
22 boys	4 (18.2 %)	17 (77.2 %)
28 girls	11 (39.2 %)	23 (82.1 %)
30 healthy premature	9 (30.0 %)	24 (80.0 %)
13 boys	2 (15.4 %)	10 (76.9 %)
17 girls	7 (41.2 %)	14 (82.4 %)
10 asphyctic premature	9 (90.0 %)	5 (50.0 %)
6 boys	6 (100.0 %)	3 (50.0 %)
4 girls	3 (75.0 %)	2 (50.0 %)

ference was observed. The total number of these tachycardias, grouped also according to their duration and their relative incidences (1/recording hour) are given in Table VI. The total relative incidences are practically the same in the healthy groups, but a clearly lower value is obtained in the asphyctic group. The duration is usually under 15 min. The maximal duration of this kind of sinus tachycardia was 60 min in full term infants, and 20 min in premature infants. Table VI also shows the incidences of tachycardias accompanied by T wave changes, usually lowering or inversion, and shortening of P R interval. These changes were most frequent in healthy prematures, but they were not identified in asphyctic cases at all. The most common report in the diary during the tachycardias was spontaneous crying, but they were also associated with injections, taking of blood samples physical examination, controlling of temperature heart and respiratory rates, suction of mucus, and the finding of wet swaddling clothes!

Heart rate variation

All the 50 full term infants had a minimal continuous irregularity of heart rate which will be called here phasic variation. This term was characterized and introduced for long term recordings of the heart rate of newborn infants by Urbach et al. [93]. It corresponds to minimal, «normal» sinus arrhythmia but the former term is preferable because in continuous recording, the heart rate is really varying all the time, but the phenomenon is not a real arrhythmia. The criteria of phasic variation can be applied directly to Arrhythmigraphic presentation [93]. In the AVSEP display this pattern is seen as a continuous horizontal movement of the terminal tail of the ECG complex; it is also heard as a fluctuation of the tone of the loudspeaker. In the AVSEP phasic variation was detected also in very high heart rates of the magnitude of 260/min, where the Arrhythmigraph failed to demonstrate the phenomenon.

T. b1. VI Incidence of tachycardias with heart rate of more than 170/min and association of T waves and P-R interval changes with them in ECG tape recordings of 30 newborn infants.

Material	Number of cases	Duration of recording (h)	Number of tachycardias (Number of tachycardias/ recording hour)				Total	Number of tachycardias with T wave changes (No./ recording hour)	Total	Number of tachycardias with changes of P R interval (No./recording hour)
			Duration < 3 min	Duration 3-15 min	Duration > 15 min	Total				
Full term newborn	50	1308	220 (0.166)	174 (0.133)	46 (0.037)	440 (0.333)	31 (0.077)	21 (0.053)		
Healthy premature newborn	30	514	121 (0.137)	53 (0.103)	14 (0.027)	180 (0.310)	41 (0.079)	24 (0.128)		
Asphyctic premature newborn	19	129	2 (0.016)	8 (0.062)	4 (0.031)	14 (0.109)	0	9		

In the healthy premature group, phasic variation was present in 26 infants (86.6 %). Four of these 26 cases had no variation during the first hours of recording. This normal variation of heart rate was found in 3 asphyctic prematures (30 %), and in one of them it developed only after an 11-hour recording at the age of 19 hours.

There were 11 cases (7 full-term, 3 healthy premature infants and one asphyctic baby) with marked phasic variation. In the scanner display it resembled ectopic arrhythmia so much that this could be excluded only by writing out the recording on paper. In 3 full-term infants the periods of marked phasic variation were longer than 2 hours, but in all other infants the duration of these periods was only a couple of minutes. Marked phasic variation mostly appeared in connection with the lowest basal heart rate levels of 90-130/min, but there were 2 premature infants whose basal heart rates of 143/min were suddenly interrupted by short periods of phasic variation one of them even had fixed heart rate.

The contrast phenomenon to phasic variation, fixed heart rate [73] was found in 16 infants. All of them were premature ones. The segments of fixed heart rate and normal phasic variation in the premature material are presented in Fig 10. In 10 of these children, 4 healthy and 6 asphyctic cases, only fixed rate was observed almost all of them had a history of complicated delivery (2 toxæmias, one maternal uraemia, 2 breech presentations, 3 cases of ablatio placentae, and one retentio placentae partialis). In 2 of them, delivery was by caesarean section. 4 healthy and 2 asphyctic prematures had both fixed rate pattern

and phasic variation in their recordings. There was only one abnormality breech presentation, in this group. Maternal hypertension had no relation to the incidence of the fixed heart rate pattern. When the whole group of infants with fixed cardiac rate was taken into consideration, it was found that 12 of them belonged to the birth weight group I (weight below 2000 g) that 10 of them were children of primiparas, and that the mean Apgar score was lower than that of other prematures (6 for the fixed rate group 7 for the others). The difference of the distribution of infants with fixed rate between the weight groups I and II is highly significant.

Effect of first feeding on heart rate

The basal heart rates of 24 full term infants representing the hour of first feeding together with one and two hours before and after it are shown in Fig 11. The means of these values are expressed as a heavy curve which has a minimum one hour before the meal, and a maximum one hour after it. Thus, eating produces a rise of basal heart rate but no other changes

are found. The difference between the minimum and maximum values of the basal heart rate curve proved to be statistically significant. The first feeding was performed approximately 24 hours after birth in full term infants. The phenomenon was not studied in premature material because of variation in the moment of first feeding

Effect of diurnal variation on heart rate

In order to find out whether diurnal variation had any effect on the mean basal heart rate of the material, each recording was divided into 3-hour segments according to the time of the day the recording was performed. Thus 8 segments per day were obtained and the mean values of the heart rate of corresponding segments were calculated in the whole material. The values were between 124 and 127/min, the highest values being found during the first three segments of the day (between 00 00 and 09 00). The differences could not be statistically tested, but it can be stated that this distribution does not distort the basal heart rate curve plotted as a function of age



Fig. 10 Segments of phasic variation (light line) and fixed heart rate (heavy line) in the recordings of 40 premature infants. Asphyctic cases have been marked on the vertical axis.

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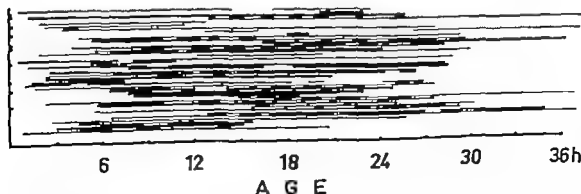


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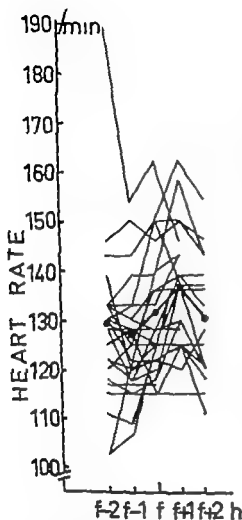


Fig. 11. Basal heart rates of 24 full-term infants during the hour of first feeding (f), and one and two hours before (f-1, f-2) and after feeding (f+1, f+2). The heavy line represents the mean basal heart rate of the cases.

Discussion

The mean cardiac rate of newborn infants has been reported to be on a uniform level in most conventional ECG studies, as well as in the tape recording investigation of Morgan & Guntheroth [37] as also in the present study. Although, for practical reasons, infor-

mation concerning the electrocardiographic pattern of the first 30 minutes is lacking in the present investigation, the declining mean basal heart rate during the first 6 hour period is in agreement with the long-term recordings of Desmond et al. [18], and the present results also confirm the slow gradual cardiac acceleration during the period from 6 to 24 hours reported by Contis & Land [12] and Vallbona et al. [100]. On the basis of conventional studies it has been believed that premature infants have a higher heart rate than full term. No differences were found in this study between the basal rate levels of term babies and healthy and asphyctic premature babies, but the levels of small premature and large full term newborn were significantly higher than those of infants weighing 2000-3500 g. The postdelivery dip of the basal rate curve was more marked in the latter group than in the former. Walsh has also noted that small prematures have significantly higher heart rates [105], but she could not find any difference between those of small and large full-term newborns [106]. The cardiac frequency of distressed infants does not differ from that of normal newborns, although the means of distressed and premature infants are higher than that of full-term [41]. However, mean heart rate does not appear to have the same meaning as basal heart rate: the former is an arithmetic calculation of a couple of pulses, the latter represents the level of existing basic cardiac activity fluctuations from which can be produced by means of various stimuli [10, 29].

The first postdelivery cardiac acceleration period [12, 18] was not included into the present study. Tendency to

and phasic variation in their recordings. There was only one abnormality breech presentation, in this group. Maternal hypertension had no relation to the incidence of the fixed heart rate pattern. When the whole group of infants with fixed cardiac rate was taken into consideration, it was found that 12 of them belonged to the birth weight group I (weight below 2000 g) that 10 of them were children of primiparas, and that the mean Apgar score was lower than that of other prematures (6 for the fixed rate group 7 for the others). The difference of the distribution of infants with fixed rate between the weight groups I and II is highly significant.

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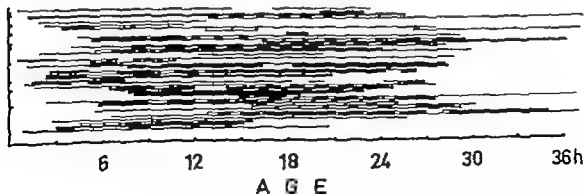


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needed. According to the present experiences, a continuous stimulation cannot be produced by volume difference originating from early or late clamping of the cord. In the full-term material early clamping of the cord caused a slightly lower mean basal heart rate during the observation period, but the difference was not significant. This is in agreement with the results of conventional recordings [108, 109].

It is also interesting that in the whole material there were 14 per cent of infants with a basal cardiac rate of more than 125/min all the time, and that most of these were premature. On the other hand, the material included 18 per cent of infants with an exceptionally slow neonatal basal heart rate. Are there sympathotonic and vagotonic newborn? Is the autonomic tonus related to immaturity or birth weight or sex? These questions still need more investigation.

Although the basal heart rate level of asphyctic infants did not significantly differ from that of healthy premature, the tendency of asphyctic babies to marked bradycardias, deeper (more frequent, and of longer duration, is clearly demonstrated. The asphyctic group is rather small for conclusions, but the results are in agreement with those of Rudolph et al. [73] and Urbach et al. [83], where V shaped short decelerations were found in continuous heart rate recordings of healthy children and bradycardias lasting 30 seconds or more preceded grave asphyxia. A considerable bradycardia and decrease of the aortic blood pressure has also been reported to follow the clamping of the umbilical cord of asphyctic lambs [85].

The phasic variation pattern (sinus arrhythmia, fluctuation of heart rate) was present in all full-term babies from the very beginning. Most of the premature also had this variation. Some of the premature, especially those weighing less than 2000 g, had a tendency to fixed heart rate pattern which has earlier been described by Rudolph et al. [73] Vallibona et al. [100] and Urbach et al. [83]. According to these publications and the present results, fixed heart rate is a typical finding of small, asphyctic premature with a history of complicated delivery. This pattern may be broken by a grave bradycardia, but it may also be transformed to phasic variation as the child recovers from asphyxia. The tachycardic reactivity of the heart rate to external stimuli is lost in this condition. A common opinion of the cause of fixed pattern is that the nervous regulation of the sinus rhythm is eliminated for some reason, perhaps by medullary depression. Some of the medullary or other nervous regulatory centres must be still operating, because bradycardias are produced, and according to our clinical observations these bradycardias can be prevented with atropine.

The first feeding had a fairly clear accelerating effect on the heart rate for an hour or two. The direct effect of feeding, i.e. the vagal effect of filling of the stomach described by Phillips et al. [86] in premature infants, could not be demonstrated because of disturbances in the recording. Like an elevated blood pressure during sucking [33] the accelerated heart rate may originate from endogenous haemodynamic stimulation, but more likely it is caused by the irritating effect of

wide fluctuations of heart rate developed rapidly in 2—3 hours in the present material, as has been earlier described [18 29]. The excursions of the rate deviation of healthy premature infants seem to be lower and disposition to maximal tachycardias at first develops more slowly. This may be an expression of the slower reactivity of immature infants claimed by Desmond et al. [18]. The tachycardic reactivity of asphyctic cases seems to be even more impaired, because the tachycardias never reached the values of healthy premature newborns, and the relative incidence and duration of tachycardias with a frequency of more than 170/min among the asphyctic babies were lower than among the healthy newborns. The limit 170/min was chosen arbitrarily in order to qualify a tachycardic heart rate level differing enough from the basal heart rate area. It is known that young children can well tolerate heart rates exceeding 170/min, but it is surprising that a newly born infant can keep his cardiac frequency over this value for many minutes, up to 20 minutes in the premature and up to 60 minutes in the full term material. Peak values of 200/min have been reported for newborn infants [12, 18 47 84 92, 102]. Not infrequently this level was exceeded in the present series, where peak values of 260/min for a term infant, and 222/min for a premature one were discovered. Most of the tachycardias occurred in connection with spontaneous crying, the heart rate pattern being similar to the previous descriptions [18 93]. Injections, examinations, and therapeutic procedures were performed much more in the premature, and it is therefore important to observe that these disturbing

factors do not cause sufficient irritation to provoke different kinds of heart rate patterns.

In the present series bradycardias of short duration were found in both full term and premature infants. The limit 90/min is empirical because during analysis it was found that short drops below this level were exceptional enough to be collected and studied more closely in the recording and that bradycardias with longer duration fell below this value. These very short neonatal bradycardias have been described earlier [18 48 55 66 93 99 105]. They were very common in the premature material of Morgan et al. [55] but were not detected in the comparative investigation of Morgan & Guntheroth concerning full term babies [57]. They have been detected following clamping of the umbilical cord, suction of the hypopharynx, defecation, hiccup, yawn, and nasogastric intubation in term infants [48 99]. Phillips et al. produced bradycardias by means of pressing the anterior fontanel, and by ocular and carotid sinus stimulation, and this was also the response of feeding, especially in small prematures [66]. In the last mentioned articles these deceleration-acceleration alterations of neonatal heart rate have been supposed to reflect the response of the cardiac pacemaker to stimuli of cardioregulatory centres, which, in turn, are under the control of various detector mechanisms. Thus a special servomechanism for the haemodynamics of newborn infants is formed. Vallbona et al. found no correlation between arterial blood pressure and these heart rate fluctuations [99]. It was supposed that volume receptor stimulation produced a cardioinhibitory effect after clamping of the cord, but relatively large volumes would be

ARRHYTHMIAS

Results

Cardiac arrhythmias detected in the maternal, 50 full term and 40 premature infants, by ECG tape recording are presented in Table VII, and their occurrence during the first 36 hours is shown in Fig. 12.

None of the cases with neonatal arrhythmias had a history of foetal cardiac arrhythmias. The distribution of neonatal arrhythmias was equal between the infants of primiparas and multiparas, between the group with maternal hypertension and that of non-hypertensive mothers, and between the full term groups with early and late clamping of the umbilical cord. No significant differences were found between the arrhythmic and non-arrhythmic group in respect to serum calcium and potassium concentrations. The dis-

tribution of cardiac irregularities between the three Apgar score groups, 0-3, 4-7 and 8-10 was not equal. In the last two groups there were approximately equal amounts of rhythm disturbances, but no arrhythmias were detected in the first group when the 10 asphyctic prematures were excluded. Nursing procedures had no effect on the regularity of cardiac activation.

The distribution of cases with cardiac arrhythmias in 80 healthy newborn infants between 4 birth weight groups is presented in Fig. 12. The columns indicate relative incidences of different arrhythmias. The group with the highest birth weight (IV) included the largest relative number of arrhythmias. Compared with other groups, the difference is highly significant. The supraventricular arrhythmias were distributed equally between the four groups. The same was the case with nodal beats in groups I, II, and III.

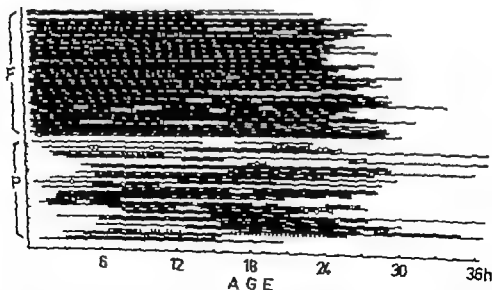


Fig. 12. Occurrence of cardiac arrhythmias, in the recordings of 80 full-term (F) and 40 premature (P) infants. Asphyctic cases have been marked on the vertical axis. \times sinus arrest, — supraventricular arrhythmia, \circ wandering pacemaker, \square nodal rhythms, \sim ventricular rhythm, - - - supraventricular extrasystoles, and \diamond ventricular extrasystoles.

increased motility of the gastrointestinal tract, because most of the infants were very restless and cried for long periods after the first feeding.

There was a low positive correlation between the heart rate and rectal temperature at the beginning of recording. The temperature was not monitored continuously in the present study but according to Contis & Lind [12] and Desmond et al. [18] the decrease of heart rate and the slight lowering of temperature of the subject are simultaneous phenomena. The possible effect of diurnal variation on the basal heart

rate was checked. No clear differences between the mean cardiac rates in different time periods of the first day of life could be demonstrated. This calculation could not be tested statistically but it can be said that the values are so equal, that this variation does not disturb the formation of the mean basal heart curve plotted as a function of age. This calculation gives the impression that a newly born infant is haemodynamically rather resistant to the rather feeble external stimuli caused by diurnal rhythm during the first day of life.

Table VII. Number of cases with cardiac arrhythmias in 50 full term, 30 healthy premature, and 10 asphyctic premature newborn infants.

Arrhythmia	Full term	Premature	
		healthy	asphyctic
Sinoatrial block	—	—	1
Supraventricular arrhythmia	6	4	—
Wandering pacemaker	4	—	2
Nodal rhythms	5	2	7
Ventricular rhythm	—	—	3
Supraventricular extrasystoles	3	—	—
Ventricular extrasystoles	1	—	—
Total	19	6	13

ARRHYTHMIAS

Results

Cardiac arrhythmias detected in the material, 80 full-term and 40 premature infants, by ECG tape recording are presented in Table VII, and their occurrence during the first 36 hours is shown in Fig. 12.

None of the cases with neonatal arrhythmias had a history of foetal cardiac arrhythmias. The distribution of neonatal arrhythmias was equal between the infants of primiparas and multiparas, between the group with maternal hypertension and that of non-hypertensive mothers, and between the full-term groups with early and late clamping of the umbilical cord. No significant differences were found between the arrhythmic and non-arrhythmic group in respect to serum calcium and potassium concentrations. The dis-

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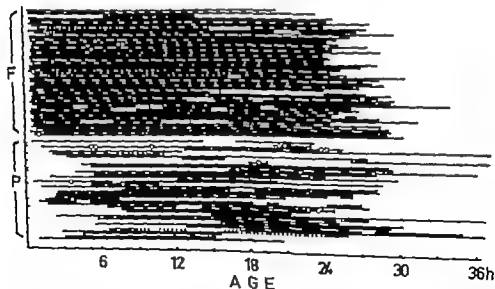


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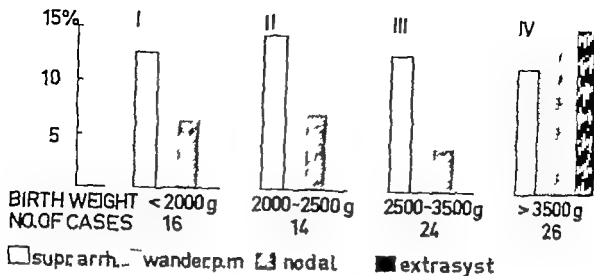


Fig. 13. Relative incidences of cardiac arrhythmias in the four birth weight groups.

Wandering pacemakers and extra systoles appeared only in group IV. The distribution of the cases with cardiac arrhythmias between the sexes in the healthy full term and premature groups is presented in Table VIII. The supraventricular arrhythmias and nodal beats occurred mainly in the girls, and the total number of the girls with rhythm irregularities was also higher than that of the boys. This difference is almost significant. Because of these results, the sex distribution of group IV (birth weight > 3500 g) was checked. The group included 13 boys and 13 girls. Thus the concentration of ar

rhythmias in females did not cause the accumulation of these in the highest birth weight group.

The term supraventricular arrhythmia is not generally used in electrocardiography. This arrhythmia, described by Michaëlisson in newborn infants, consists of a minimal variation of P R duration usually accompanied by a small fluctuation in the shape and amplitude of the P wave [34]. In the healthy material, this irregularity appeared in long successions in 10 babies.

An example of wandering pacemaker in a 2 hour-old boy is shown in Fig

Table VIII. Distribution of cardiac arrhythmias between boys and girls in 54 full term, and 38 healthy premature newborn infants.

Arrhythmia	Boys		Girls	
	Full term	Premature	Full-term	Premature
Supraventricular arrhythmia	—	1	6	3
Wandering pacemaker	4	—	—	—
Nodal rhythms	—	—	5	2
Supraventricular extrasystole	1	—	2	—
Ventricular extrasystole	1	—	—	—
Total	6	1	13	5
Total material	22	13	28	17

14, where a gradual inversion of P_{T_2} with simultaneous prolongation of P R duration is to be seen. This change was reversible. Wandering pacemakers were detected 3 times in one, twice in one, and once in 2 full-term infants during the first 12 hours after birth. During these rapid rhythm alterations the babies were usually reported to be restless.

Nodal rhythm irregularities were detected in 5 full-term and 2 healthy premature infants. All of them were girls. In 6 cases, nodal beats occurred in the middle of sinus bradycardia, although in 3 cases only the heart rate fell below 90/min. In one full-term infant a few nodal beats were found at a normal heart rate level. These nodal beats were identical with those described in the report of Morgan et al. with a sudden shortening of P R interval, but without inversion of P deflection [33]. Thus, it would be preferable to call this change simple atrio-ventricular (A V) dissociation, to distinguish it from the real nodal rhythms with retrograde atrial conduction found in asphyctic infants.

Supraventricular premature beats

were recorded in one full term boy and 2 full-term girls. These arrhythmias were met in long successions during the first 18 hours. An example is presented in Fig 15. Because the ectopic beats had a nearly normal configuration, it was sometimes difficult to identify them in the scanner analysis. The pattern is, however characterized by varying tails of base line in AVSEP display and particularly by a typical irregular sound heard in the loud speaker. Only one single ventricular ectopic beat was diagnosed in the whole material. This was just before a wandering pacemaker attack in a 6 hours-old full term boy.

In 2 infants, one full-term and one premature, several periods of regular oscillation of base line at a frequency of 800–900/min were established (Fig 16). The amplitude of these minimal

In the series of 30 newborn infants examined for the comparison of conventional and tape recordings (section I of this investigation) there was a 3 day-old girl with ventricular premature beats. This arrhythmia was not present in conventional recordings, but it was easily detected in the tape recording (see Fig. 6).

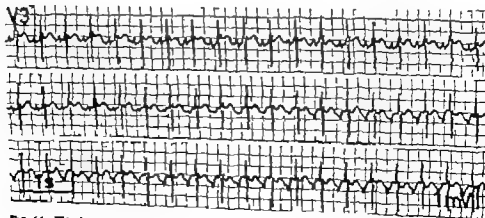


Fig 14. Wandering pacemaker in two-hour full-term boy. Electrocardiocharter 330 reproduction.

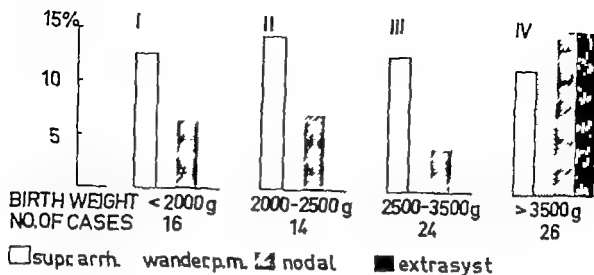


Fig. 13 Relative incidences of cardiac arrhythmias in the four birth weight groups.

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Wandering pacemaker	4	—	—	—
Nodal rhythms	—	—	5	2
Supraventricular extrasystole	1	—	2	—
Ventricular extrasystole	1	—	—	—
Total	6	1	13	5
Total material	22	13	28	17

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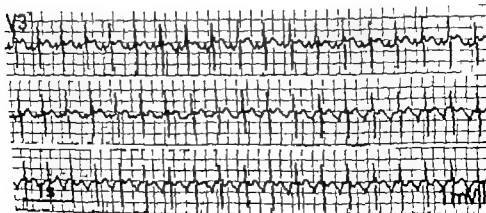


Fig. 14. Wandering pacemaker in two-hour full-term boy. Electrocardiogram 150 mm.

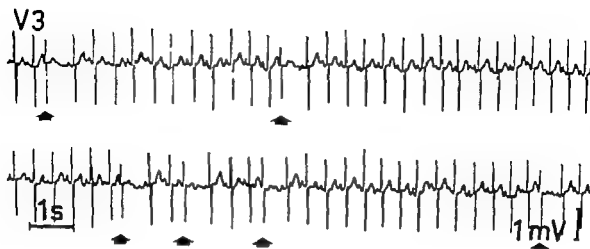


Fig. 15 Supraventricular extrasystoles in a 14 hour full term boy MV 1 reproduction.

serrations changed a little, and they interfered with the reproduction of the P wave. This condition was at first thought to be auricular fibrillation. Because the ventricular rate remained regular without alteration of frequency the phenomenon was considered to be an artifact as in an identical case in the publication of Landtman [35]. The origin of this phenomenon remains unclear.

The arrhythmias in pathological premature infants will be described in the chapter on asphyctic cases. The conduction disturbances are presented in the chapter dealing with patterns of electrocardiographic intervals.

Discussion

The results presented here are in contrast to the findings obtained with tape recording technique by Morgan et al. [55] and Morgan & Guntheroth [57]. The only real arrhythmia typical of premature newborn infants in these articles was nodal escape during marked sinus bradycardia, and it was not detected in full term babies at all. In the present study the incidence of

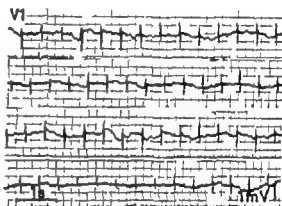


Fig. 16 Oscillating base line, probably artifact, in a 13-hour full term girl. Composite Electocardioscanner 631 reproduction.

this A V dissociation was highest in the full term infants with a birth weight of more than 3500 g. An occasional premature beat was observed in a few infants by Morgan & Guntheroth however in the present recordings, extrasystoles mainly appeared over long periods, except for one ventricular ectopic beat. In the long term ECG study of Vallbona et al. 8 cases with sporadic extrasystoles during the first 8 hours after birth were detected in the material of 57 newborn infants [99]. It is indeed possible that occasional ectopic beats resembling sinus beats can be missed in the scanning

as has been supposed previously [35, 55]. The discrepancies mentioned above may be due to the different age distribution and also to the rather small number of arrhythmic cases in the materials.

The total number of infants with real cardiac rhythm irregularities (16 full-term and 7 healthy premature babies), in the material of 111 healthy newborns is, surprisingly of the same magnitude as in the conventional ECG studies of Burghard & Wunnerlich [8], Balhø [67] and Michaësson [64] but it is appreciably higher than in most conventional investigations. The same kind of arrhythmias, mostly ectopic pacemakers, have been found by means of conventional ECG as in the present investigation. However most of the premature beats have been ventricular [60, 72, 82, 106] whereas they are mainly supraventricular in the present material.

The interesting difference between the sexes has not been found earlier. Although the difference seems to be clear and almost significant ($p < 0.05$) the material and the number of arrhythmias are very low for definitive conclusions.

According to the present investigation, most irregularities are to be found in full term infants, especially in those with high birth weight. In general these disturbances are symptom free, except for *asthenes* during pacemaker alterations. They do not correlate with obstetric history or with the serum calcium or potassium content of the infant, they do not occur in infants with low Apgar scores. Nursing procedures had no effect on the incidence of arrhythmias. Phillips et al.

reported marked sinus depression, P wave changes, and shifting of the pacemaker ensuing from oculobulbar and carotid sinus stimulation, and pressure over the anterior fontanel in premature infants [66]. Occasionally these were associated with apnoeic periods of phasic respiration, although no clear cut relationship between cardiac and spontaneous respiratory irregularities was defined. We did not detect any arrhythmias except sinus bradycardia in association with phasic respiration [15]. Vallbois et al. succeeded in provoking extrasystoles by thumbing the foot in one newly born infant, and in most cases a transient bradycardia was the response to this kind of cutaneous stimulus [99]. Contrary to the report of Phillips et al. [66], feeding did not produce any rhythm irregularities in the present material in the premature, but the ECG corresponding feeding time in full-term babies could not be analysed because of recording disturbances.

Arrhythmias have been considered as evidence of prominent reactivity of the neonatal developing autonomic nervous system [55, 64, 99]. The vagus sensitizing effect of digitalis, increasing tendency to cardiac rhythm irregularities, has been stressed by Levine & Blumenthal [45]. None of the infants in the present series had received digitalis. In the light of the present investigation, the cardiac arrhythmias described here seem to be a variation of neonatal cardiac action, causing no serious disturbances. If there really are differences between sexes and birth weight groups in the tonus of the autonomic nervous system, investigation of other functions reflecting this tonus during the first days of life is needed.

DURATIONS OF P WAVE, P R, QRS AND Q-T INTERVALS

Results

Duration of P wave

The alterations of mean P wave duration during the first 27 hours in full term and healthy premature infants are presented in Fig 17. The mean values and ranges of both groups at the age of 2 and 24 hours are compared in Table IX. In full term infants the P wave duration was longer than in the premature group during the first 6 hours but this difference was not statistically significant. Generally the P wave duration was of the same magnitude in all the 3 leads, but if

different values were detected at the same time the longest of them was chosen for calculations. The same rule was obeyed in the measurement of the other intervals. A gradual shortening occurred during the observation time in both groups, but it was steeper in full term infants. The P wave duration was not dependent on heart rate, but sometimes a minimal shortening was established in association with very high heart rate. This was not a regular response to tachycardia even in the same infant, and the phenomenon is difficult to investigate because of the fusion of P and T waves in high heart frequencies. The time of clamping of the umbilical cord had no effect on P wave duration.

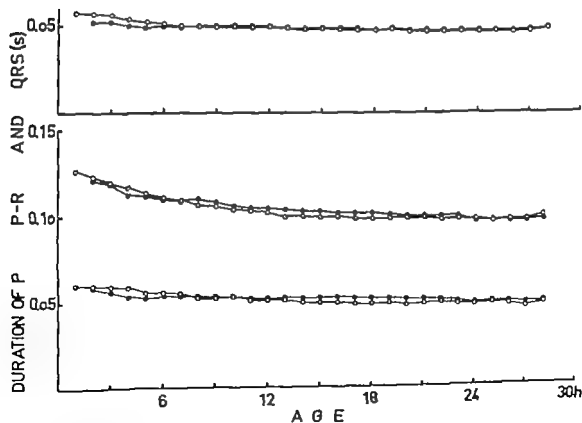


Fig. 17 Mean durations of P wave, P R, and QRS intervals during the observation time in 50 full term (O—O) and 30 healthy premature (●—●) infants.

T b) IX. Durations of P wave, P R, QRS and Q-Tc intervals on the 2nd and 24th hours of life in 50 full-term and 30 healthy premature infants. The maximal values found in the 2 chest leads have been taken for calculations.

Material	Age (h)	P duration ()		P R interval ()		QRS duration ()		Q-T ()	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
50 full-term	2	0.061	0.03-0.08	0.123	0.09-0.17	0.026	0.02-0.07	0.440	0.37-0.49
30 premature	2	0.060	0.04-0.07	0.122	0.09-0.14	0.033	0.02-0.06	0.441	0.43-0.46
50 full-term	24	0.048	0.03-0.06	0.097	0.08-0.15	0.047	0.04-0.06	0.430	0.37-0.49
30 premature	24	0.039	0.04-0.06	0.097	0.06-0.11	0.047	0.04-0.06	0.443	0.40-0.49

Duration of P R interval

The behaviour of P R interval during the first day of life in full-term and healthy prematures is shown in Fig. 17 and the 2 hour and 24-hour means and ranges for both materials are presented in Table IX. A clear decrease of the duration of this interval is demonstrated in both presentations. This decrease occurred in the material during the first 14 hours. No significant differences could be noted between the values of full term and healthy premature infants, and between those of the 4 birth weight groups. The values of the group with early clamped umbilical cords were lower than those of late clamped during the whole observation period. This difference proved to be statistically significant during the first 4 hours of life. Later the values of the early and late clamped groups were more equal. When the curves of P wave duration and P R interval duration are compared in Fig 17 the prolongation of P R interval seems to be caused by the prolongation of P R segment and not by that of P wave duration.

The maximal duration of P R interval was 0.18 s in a full-term infant during the first hour of life. If values of 0.14 s or more are regarded as criteria of first degree A V block as in the study of Morgan et al. [35] there were 11 such cases in the full-term material, and 3 in the premature group, all of whom were healthy. But in all of these 14 infants, a shortening of P R interval below 0.14 s occurred during the recording time. The only real A V block in the whole material was a reversible 2:1 A V block during an asphyctic bradycardia in a 24 hour-old premature boy.

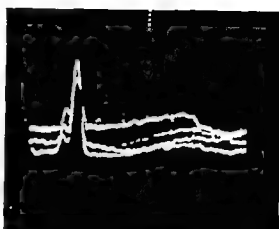
A minimal shortening of 0.01 s was sometimes, but not constantly found in association with tachycardia of more than 170/min. The incidence of tachycardia with shortening of P R interval among all the tachycardias, was approximately 5 per cent in full term, and 13 per cent in healthy premature groups (Table VI). These changes were not detected in connection with every tachycardia of the same degree in the same infant. No linear relationship could be generally demonstrated between P R interval duration and heart rate.

Duration of QRS interval

Curves of mean QRS intervals for full term and healthy premature newborns are presented in Fig 17 and the 2 hour and 24-hour values are compared in Table IX. It can be seen that this interval too shortened in both groups during the 8 hours after birth, and shortening was more prominent in the full term group. However no statistically significant differences between the values of full term and healthy prematures could be demonstrated. The infants with late clamped umbilical cords had significantly longer QRS duration during the first 2 hours than those with early clamped cords. The heart rate had no effect on the QRS interval. No abrupt alterations of this interval could be detected during the ECG recordings except in terminal asphyxia.

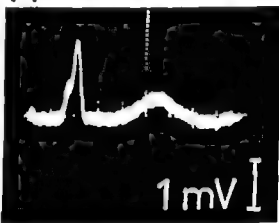
In two full term boys the duration of the QRS interval was 0.07 s in the first hour of life and the R_{V_1} wave was notched. Thus an incomplete right bundle branch block configuration was formed. However the QRS interval shortened later to 0.05 s, and the

V1



0.5 s

V1



1 mV

Fig. 18. The decrease of QRS duration, and notching of R wave during the first hours of life in a full term boy. The upper recording at the age of 30 min, the lower at the age of 4 h.

notching of the R_{V_1} became less marked, as can be seen in Fig 18. Thus it is questionable whether it is at all justified to call this extremely prolonged QRS a RBBB. QRS intervals of 0.07 s were found in 4 additional infants during the first hour of life but in these cases no notching of the R wave was present. In the present recording the QRS of premature infants was never longer than 0.06 s, but the longest

intervals were detected during the first hours of life, and these values were lacking in many premature babies.

Duration of Q-T interval

Because the duration of the Q-T interval is very sensitive to heart rate alterations, this effect of heart rate was eliminated in the classical manner by correcting the Q-T interval according to Bazett's formula

$$Q-Tc = \frac{Q-T \text{ measured}}{\sqrt{\text{cycle length}}}$$

[6] The 2-hour and 24-hour values of Q-Tc are shown in Table IX. The Q-Tc values of full-term and healthy premature infants were practically equal during the first 3 hours, but from the 6th hour of life, the mean values of healthy prematures were significantly higher than those of full term babies, the difference being of the same magnitude as that given in Table IX for the age of 24 hours. A transitive prolongation of Q-Tc occurred during the 3rd–5th hours of life, the mean Q-Tc was 0.44 s in the 2nd hour in

both groups of infants, the value of 0.448 s was achieved in the full term, and that of 0.452 s in premature in the 4th hour. The mean value of the full-term material gradually decreased until the stable level of 0.43 s was reached. The maximal mean Q-Tc values were achieved in the 6th–7th hours in the premature group, and thereafter the values remained on the statistically significantly higher level of 0.445–0.45 s. The Q-Tc curves for the 4 birth weight groups are presented in Fig. 19. The values of groups I, II, and III were significantly higher than those of group IV during the whole observation time. No relationship between the alterations of the Q-Tc and the other intervals appeared to be present.

The moment of cord clamping produced no effect on the Q-Tc interval. No linear relationship was detected between the durations of P wave, P R interval, QRS interval, and Q-Tc, and the Apgar score, maternal hypertension or the parameters listed in Table IV.

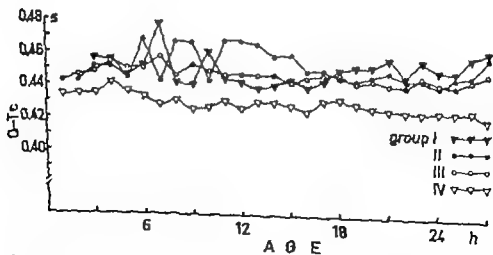


Fig. 19 Mean Q-T values of healthy infants with birth weight of (I) < 2000 g, (II) 2000–2500 g, (III) 2500–3500 g, and (IV) > 3500 g.

In cases with hyperpotassaemia (serum potassium more than 7 mEq/l) no prolongations of P wave duration, P R interval, or QRS interval were found, except in one full term girl with a serum potassium of 7.4 mEq/l who had a P wave duration of 0.08 s and P R interval of 0.18 s, but the other intervals were normal. There were still more elevated serum potassium concentrations, up to 8.9 mEq/l without prolonged intervals, at the beginning of the recording in premature infants. The slightly elevated serum calcium concentration up to 13.1 mg/100 ml had no effect on the Q-Tc. No correlation was established between the rectal temperature at the beginning of the recording, and the initial Q-Tc value.

Discussion

The results concerning means, and ranges of duration of P wave, and P R interval, are in agreement with the results obtained on the first day of life with conventional ECG technique in full term and premature infants, although the measurements were made in standard lead II in these publications [14 20 22 24 42, 54 56 72, 101 102, 112]. The initial prolongation of these intervals has been reported by Mäkelä [54] Walsh [102] and Jäglekl et al. [39] but the present study proves that gradual shortening of P wave and particularly of P R interval, take place during the first 14 hours after birth. There are significant differences between the P R and QRS intervals of the groups with early and late clamping of the cord, during the first hours, which is in agreement with the results of Walsh [108 109]. However contrary to the

results of Walsh, no difference exists between the corresponding values of P wave duration. A discrepancy also exists between the reports of Walsh [102, 108, 109] and the present results, concerning the role of P wave duration in prolongation of the P R interval.

As possible causes for the prolongation of these intervals, left atrial hypertrophy or dilatation, vagal tone and volume load of the heart have been proposed [102 108 109]. Elevated serum potassium content has also been held responsible for prolongation of P and P R interval durations [58]. In the present series, there was only one case with extreme prolongation of these segments, associated with moderate hyperpotassaemia. An increase in vagal activity has been reported to result from volume loading of the atria [64]. At the present time we do not know whether these atrial reflexes are mature in newborn infants, but it is possible that the more prominent prolongation of the P R interval, compared with that of P wave duration, may be of vagal origin. The question of whether the stimulus of vagal tone is volume load of the left atrium, resulting from adjustments of the neonatal pulmonary circulation, still remains unresolved.

Contradictory reports concerning the relationship between heart rate, and durations of P wave, and P R interval, have been presented [3 23 102, 112]. According to the present observations, shortening of these intervals may occur quite randomly in association with tachycardias, reflecting perhaps, the alternating control of the autonomic nervous system upon the electric activation of the heart.

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tional investigations [20, 22, 24, 34, 69, 72]. A significant difference between the longer QRS interval, of infants less than 30 min old, and the shorter one of infants more than 4 hours old, has been described by Walsh [103]. According to the present study the shortening of the QRS interval takes place during the first 12 hours, it is most prominent during the first 6 hours, and the decrease is steeper in full-term infants, although there are no significant differences between the values of full-term and premature babies. The changes are fairly similar to those of the P wave and P-R interval durations. The same regulating factors have been discussed as being responsible for shortenings of all these intervals, by Walsh, who has also found that no dependence exists between the decrease of the QRS interval, and that of heart volume in roentgenograms [103]. The present results offer no more information concerning the etiology of these alterations of the QRS interval.

The present values of Q-Tc are longer than those of Craige & Harned [14] but equal to those of Walsh [103] and Fonseca Costa et al [22]. This may be due to the difficulty of measuring the Q-T interval exactly. The present results confirm the observation of Walsh, concerning the non-dependence

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Table X. Means and ranges of P R, S and T wave voltages at the age of 2 and 24 hours in 50 full term and 36 healthy premature infants.

P wave (initial/terminal deflection)

Material	Age (h)	V 1			V 3			V 5		
		mean (mV)	range (mV)	mean (mV)	range (mV)	mean (mV)	range (mV)	mean (mV)	range (mV)	range (mV)
Full term	2	0.13/-0.06	0.05-0.20/-0.05-0.10	0.19	0.10-0.40	0.14	0.05-0.30	0.14	0.05-0.30	
	24	0.14/-0.06	0.05-0.20/-0.05-0.10	0.19	0.10-0.30	0.13	0.05-0.30	0.13	0.05-0.30	
Premature	2	0.14/-0.06	0.05-0.20/-0.05-0.10	0.13	0.05-0.30	0.15	0.05-0.30	0.15	0.05-0.30	
	24	0.11/-0.07	0.05-0.20/-0.05-0.10	0.11	0.05-0.20	0.11	0.05-0.20	0.11	0.05-0.20	

R wave

Full term	2	1.33	0.80-1.90	1.45	0.60-2.30	0.91	0.10-1.50
	24	1.26	0.60-1.90	1.35	0.60-2.00	0.87	0.10-1.30
Premature	2	1.06	0.70-1.50	1.23	0.50-2.00	1.07	0.40-1.90
	24	0.88	0.50-1.40	0.88	0.40-1.40	0.62	0.20-1.00

S wave

Full term	2	0.56	0.10-1.20	1.48	0.80-2.00	1.22	0.20-1.70
	24	0.57	0.10-1.30	1.49	0.90-1.90	1.22	0.20-1.70
Premature	2	0.67	0.10-1.20	1.22	0.40-1.90	0.90	0.60-1.10
	24	0.62	0.10-1.30	1.12	0.90-1.50	0.57	0.20-0.90

T wave (initial/terminal deflection)

Full term	2	0.22/-	-0.10-0.50/-	0.26/-0.08	-0.20-0.70/-0.10-0.10	0.16/-	-0.2-0.6/-
	24	0.33/-	0.10-0.10/-	0.21/0.10	-0.40-0.90/0.10	-0.01/-0.10	-0.4-0.4/-0.10
Premature	2	0.12/-	-0.20-0.30/-	-0.01/0.10	-0.40-0.40/0.10	0.06/-0.10	-0.2-0.2/-0.10
	24	-0.02/-	-0.40-0.40/-	-0.15/0.00	-0.80-0.10/-0.10-0.10	-0.02/-0.10	-0.3-0.2/-0.10

VOLTAGE PATTERNS

Results

P wave

The means and ranges of the P wave in the V1, V3, and V5 leads, for the 2nd and 24th hours of life, are given in Table X. The P_{V1} was mostly diphasic, with an initial positive, and a terminal negative deflection. The P_{V3} was always positive, and usually notched. The calculations were made according to the higher peak of the P_{V3} wave. The P_{V5} was always a round, very seldom notched, upright deflection. The shape, and magnitude of the P wave remained stable in all leads during the observation period. Generally the mean P wave values of the full term group were higher than those of the premature group, but this difference was not statistically significant. The moment of clamping of the umbilical cord had no effect on the P wave configuration or magnitude. Besides the minimal fluctuation of the P wave voltage in supra-

ventricular arrhythmia, and clear alterations of this atrial deflection in cases of wandering pacemaker variations of its shape and size were detected during tachycardias. It usually took the form of a round or notched P wave, turned reversibly into a peaked one, with a simultaneous increase of voltage. Less frequently a normal P wave became notched during tachycardia. These alterations were more common in full-term infants, but the exact incidences will not be given, for these tachycardic P wave alterations are difficult to estimate, due to the fusion of P and T or U waves

QRS complex

The configuration types of the QRS complex at the beginning of the tape recording are presented in Fig. 20 where the mean voltages and the incidences of these types are also shown. These data reflect a typical neonatal right ventricular preponderance, but electrocardiographic configuration, pe-

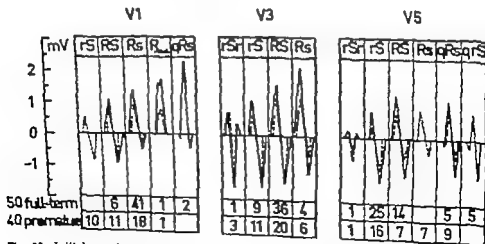


Fig. 20. Initial morphology and mean voltage of QRS complex in 36 full-term (continuous line) and 40 premature infants (interrupted line). The numerical incidences are marked under the corresponding voltage patterns.

cular to left ventricular dominance, is also found, especially in the premature group. In 3 cases, only a large, notched, R wave formed the whole ventricular depolarization complex, without S wave. An exceptional rSr pattern may be formed from rS pattern, followed by a giant post-S spike, and may therefore, be an artifact.

The Q_{V1} wave appeared with a voltage of 0.1 mV initially in 2 full term, and one premature infant, and was not met later in the recording in either of these full term babies. No Q wave was present in the V3 lead. Q_{V3} was found in 10 full term, and 9 premature infants. Its initial means are given in Fig. 20 the range being 0.1–0.5 mV in the full term and 0.1–0.2 mV in the premature infants. The voltages of Q waves remained stable during the observation time and no significant differences were detected between the values of the full term and premature material although the incidences of Q wave were very small for statistical calculations.

The 2 hour and 24-hour means and ranges of R and S waves, for both full term and premature materials, are presented in Table X. To make the material suitable for comparison, the voltages of R and S in the three chest leads were studied in 3-hour segments, after the first hour of life. As the voltages of R and S were followed, it was found that in all three chest leads a minimal decrease of amplitude of R wave occurred in the full term group, and a more marked one in the healthy premature group, whereas the S waves behaved in different ways in different leads and groups. A minimal increase of S_{V1} amplitude was found in both groups during the first 11 hours of life. The S_{V3} and S_{V5} voltages

remained constant in the full term group but a slight decrease of the S_{V3} voltage, and a clear increase of S_{V5} voltage, were established in the premature group. In the V1 lead, the R wave voltage of the full term group was, permanently highly significantly higher than that of the prematures, but no difference existed between the corresponding S waves. In the V3 lead, both the R and S wave amplitudes of the full term babies were highly significantly higher than those of the premature group. Significant differences could be demonstrated between the R wave voltages of the full term and premature groups in the V5 lead, and the differences between the higher S_{V3} values of the full term, and the lower ones of the premature proved to be highly significant.

The behaviour of the resulting mean R/S ratio in the three chest leads is presented in Fig. 21. Declining R/S₁ curves were found in both full term and healthy premature infants, but the difference between the curves did not prove to be significant. No changes appeared in the R/S ratio in the V3 lead. The R/S_{V3} of the full term babies remained rather stable, but a clear decrease in that of the prematures occurred during the observation time. The difference between the R/S_{V3} values of both groups was significant between the ages of 2–13 hours.

Thus, the neonatal electric right ventricular preponderance is demonstrable also by ECG tape recording. According to the present results, it decreases during the first hours of life, in both full term, and healthy premature infants. The behaviour of the R/S_{V3} ratio gives an impression of diminution of electric forces reflecting the left ventricular depolarization of

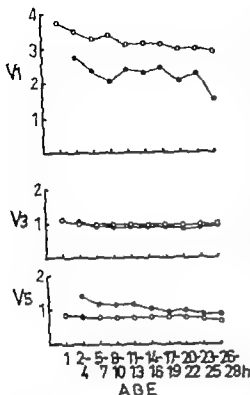


Fig. 21. Behaviour of R/S ratio in V1, V3, and V5 leads in the tape recordings of 60 healthy full-term (O—O), and 20 healthy premature infants (●—●). The values have been calculated for 3-hour periods after the initial first-hour readings.

the premature group, in contrast to that of the full-term infants. The voltages of R and S were significantly higher in the full-term infants than in the prematures, in all leads, except the voltage of S_{V1} , where no differences could be demonstrated.

No abrupt voltage alterations in these deflections were detected in the recordings, with the exception of drastic QRS d formations in terminal asphyxia.

Ventricular repolarization

S-T depressions, with an approximate magnitude of 0.1 mV (range -0.1 — -0.2 mV), were found in 8 full-

term, and 1 premature infant. S-T₁₂ deviations of the same magnitude (range -0.1 — $+0.2$ mV), in 3 full-term infants, and depressions of 0.1 mV in 4 prematures. S-T₁₂ elevations of approximately 0.15 mV (range $+0.1$ — $+0.3$ mV), appeared in 22 infants of the full term group, and of 0.1 mV (range $+0.1$ — $+0.2$ mV), in 10 premature babies. An S-T₁₂ depression of 0.1 mV was present in one premature infant. Most of the S-T deviations were junctional, and generally developed and disappeared gradually over a couple of hours, only few (2 in V1, 3 in V3, and 2 in V5 in the full term, none in premature infants) were present during the whole recording, and all except 4 were asymptomatic. Their behaviour in relation to the observation time, was not uniform at all. Because of the unclear reproduction of the S-T segment in the present tape recordings, (page 27) and the insufficient data concerning body movements of subjects in the present material, it is hardly possible to make conclusions about the changes of S-T segments as a function of time, in respect to the present investigation.

Rapid S-T alterations were detected in 4 full-term infants. Three of them occurred in association with moderate tachycardia, a 18-hour boy reported to have minimal grunting, had a reversible disappearance of 0.2 mV S-T₁₂ depression, accompanied by T wave inversion, a 21-hour girl, reported crying, had a reversible 0.1 mV depression of S-T₁₂, accompanied by T wave inversion, and a 27-hour girl, crying, had a disappearance of 0.3 mV S-T₁₂ depression, followed by a reversible 0.1 mV depression after the tachycardia, and then a gradual restoration of the original 0.3 mV depression. The

4th case, a 10-hour boy was reported to be restless, and during this time a sudden prominent nonfunctional S-T_{V3} depression was established (Fig 22) which disappeared in a couple of minutes, and was not met with later in the

recording. No rapid S-T changes were detected in the premature group, even in the asphyctic cases, except in the grotesquely deformed ECG of the dying heart.

The 2 hour and 24-hour means and ranges of the T wave amplitudes in the three chest leads are given in Table X, and the alterations of the mean T wave voltages of the full term, and healthy premature infants, during the first 27 hours, are presented in Fig 23. During the first 6 hours, the voltage of the T wave in the V1 lead gradually gained in the full term group, whereas in the same period, a gradual diminution of the T wave occurred in the prematures. There was a significant difference between the values of both groups after the 5th hour of life. The same was the case between the T_{V3} voltages of the full term, and

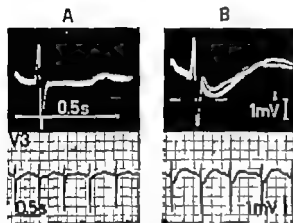


Fig. 22. Electrocardioscanner (upper) and Electrocardiocharter (lower) reproductions of basal ECG pattern (A) and marked S-T depression (B) in V3 lead in a 10-hour full term boy

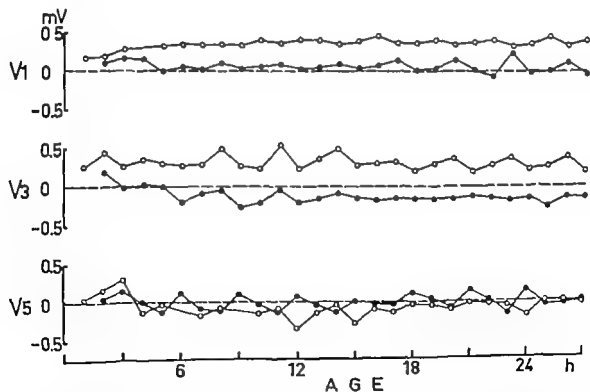


Fig. 23. Behaviour of mean T wave voltages in V1, V3 and V5 leads in the tape recordings of 50 full term (O—O) and 30 healthy premature infants (●—●) during the observation period.

healthy premature groups. In many cases, the difference was highly significant. The T_{V_3} values of the full-term tended to remain permanently positive, but those of the premature had a tendency to inversion after the first hours of life. In the V_5 lead, the T deflections of the full-term were at first mainly upright but became inverted after the 3rd hour of life. After words, however they again became more and more positive. The same tendency was present in the corresponding values of the prematures, but the wandering of the mean T_{V_3} curve fails to demonstrate the phenomenon well, because of the scattering of the values.

All the T_{V_3} deflections were monophasic, and mainly asymmetric, as has been described in conventional ECG by Sodi-Pallares et al. [84]. There were 7 full-term, and 3 premature infants, with a diphasic T_{V_3} at some time during the recording, the initial main part of which was used for the calculations for Fig. 23. The same was the case in the T_{V_5} waves, which were diphasic in 4 full term and 3 premature babies. The terminal deflection was usually lower than 0.1 mV only one full-term infant having an amplitude of 0.2 mV in the terminal part of the T_{V_3} . No statistical differences were found between the terminal T wave parts of the full term and premature groups, but the incidence was very small in the material.

The only rapid changes of T waves were those noted in association with tachycardias, an example of which is shown in Fig. 24. In most cases, this change was a flattening of the T wave, negative or positive, after a marked heart rate acceleration. The number of these changes in connection with tachy-

cardias with a rate of more than 170/min, has been given in Table VI, but there were 4 more in the full-term infants, and 2 in the prematures, following a tachycardia with a lower rate. The degree of these T wave flattenings was not proportional to the heart rate acceleration, or the duration of the tachycardia. They were not found constantly with the same cardiac rates, even in the same infant. They were not detected in the asphyctic group. Three full term infants had a T wave inversion during a tachycardia, 2 of them being accompanied by changes of the S-T segment.

V3

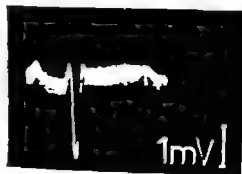


Fig. 24. Flattening of T_{V_3} wave after tachycardia in 18-hour full-term boy demonstrated in Electrocardioscanner display

U waves with an amplitude of up to 0.1 mV were detected in leads V3 and V5. $U_{1,3}$ was present in 6 full term and 4 premature infants, and $U_{1,5}$ in 10 full term, and 2 premature infants. The majority appeared during the first hours after birth, but their incidence is too small for statistical calculations. Appearance or disappearance of a U wave in some lead was not related to changes in other deflections.

Discussion

The present results of P wave amplitude are in agreement with the conventional ECG studies of Ziegler and Michaëlisson, but the voltages are in general, a little higher [112,54]. This is also to be expected, because no significant differences could be demonstrated between the P wave reproductibility of the conventional and tape recordings in section I of this investigation. Peaked right precordial P waves have been presumed by Thason (91) Vanoni [101] and Emmanouilides et al [20] to result from high pulmonary arterial pressure and right atrial overload. No uniform changes in the P wave amplitudes could be found in the present series, but pressure alterations also occur gradually after birth [21-65]. The early clamping of the cord has been reported to produce lower P_{II} voltage [108] but no effect on the precordial P waves could be established in the present study. The transformation of P waves during tachycardias is in agreement with the hypothesis of atrial volume load, but no prolongation of P wave duration was present during these tachycardic P wave alterations.

The voltage values of the QRS complex cannot be compared directly with those obtained by means of conventional recording technique, and the amplitude variations recorded must be considered with reservation, because of the attenuated voltage repeating capability of the equipment, and because of the possibilities of unhomogenous magnetic tape, and change in the subject's position.

The appearance of Q waves in the V1 and V3 leads is in agreement with the conventional studies [20, 76, 104, 110, 112]. Rarely the Q wave has been found on the right precordium, and this has been held to reflect right ventricular hypertrophy [58].

The magnitude of the present values for R and S deflections, are nearly the same as those in the corresponding conventional studies [17, 20, 76, 104, 105, 110, 112] when the present values are corrected according to the diagrams of Fig. 5. The R/S ratios are quite different because of the restricted S wave reproduction in the tape recording devices. Decreasing R wave amplitudes in the right and mid precordial chest leads after the first hour of life have been described by Walsh, and the same was the case with left precordial S waves [104]. The present results resemble the observations concerning H waves, but no alterations of the S_{T_1} wave were detected, except in the premature group. The changes in R/S ratios indicate diminution of the right ventricular electric dominance during the first day of life in both full term, and premature infants, but there is also a decrease of left ventricular forces in the premature group. A low R/S ratio in the right precordial leads has been found in association with a left to-right shunt via the ductus arteriosus, and a high R/S

ratio in left precordial leads with a lower pulmonary to systemic pressure ratio, by Emmanouilides et al. [20]. The present results are in keeping with the reports of Walsh, and Emmanouilides et al., in which these ventricular depolarization changes have been attributed to the fall of pulmonary arterial pressure, and the replacement of an initial right-to-left shunt, by a left-to-right one in the ductus arteriosus, during the first day of life [104, 20].

The values of S-T deviations are of the same magnitude as those found in conventional ECG studies. The present results support the impression that minimal deviations are found in normal newborns, but they can sometimes disappear and reappear. The cause of this cannot be explained according to the present information. The electrocardiographic changes caused by exercise, and anxiety are quite similar to the tachycardic S-T and T wave alterations of the present study and they have been thought to result from alterations in sympathetic tone [83]. The S-T depression shown in Fig. 22, resembles an ischaemic response of the S-T segment [31]. However it is impossible to say if it was caused by alteration of coronary haemodynamics, myocardial metabolism, or vegetative nervous regulation.

The T waves were mainly positive in full-term infants in the present series, and the amplitude even increased during the first hours. Thus, inversion of this deflection did not take place during the observation time, although, in some infants, the amplitude began to decrease. Stern & Lind stated that the inversion was observed in many infants during the first day of life,

although it could also occur later [86]. The amplitudes of the premature group were lower and the inversion was also earlier than in the full-term group in the present series. This is in agreement with the reports of Hubsher [38] and Fonseca Costa et al. [22]. The inversion of the right precordial T waves has been attributed to the fall of pulmonary arterial pressure by Dupuis et al. [19], and Emmanouilides et al. [20].

Both positive and negative T_{V3} waves have been reported on the first day of life, both in full term, and premature infants [17 20 22, 54 107 112]. After the first day of life the T_{V3} always becomes positive. In the present material, the mean T_{V3} was initially positive for 3 hours, then negative, and finally showed a positive tendency. The infants with negative T waves in the V6 lead were reported, in the article of Emmanouilides et al., to have higher pulmonary arterial pressures than those with positive ones [20].

The T wave amplitudes of the full term, were higher than those of the premature, in the tape recordings of leads V1 and V2. This has been reported in almost every investigation dealing with the ECG of premature infants. The voltages in the present series were of the same magnitude as the corresponding T wave voltages in the investigations mentioned above in this discussion.

The incidence and magnitude of the U wave in the present material were practically equal to those reported in newborn material by Ziegler [112], Michaélsson [34] and Walsh [107]. The appearance of the U wave was too sporadic for studies of the behaviour of this deflection during the first day of life.

Table XI. Data of the 10 asphyctic premature infants.

No.	Sex	Obstetric history	Birth weight (g)	Apgar score	Duration of tape recording	Serum K (mEq/l)	ECG findings	Response
1	f	normal	920	4	9 h — min	8	sinusoidal block	expired later*
2	m	breech delivery	1100	7	2 h 50 min	—	fixed rate, marked bradycardia, wandering pacemaker nodal and ventricular rhythm	expired during recording*
3	m	normal	1280	8	19 h 22 min	5.7	fixed rate at the beginning, initial 1° A V block	expired later*
4	m	breech delivery	1320	1	1 h 11 min	—	fixed rate marked bradycardia, nodal, and ventricular rhythm	expired during recording*
5	f	normal	1450	10	18 h 10 min	4.8	fixed rate, bradycardic rate, marked bradycardia, nodal and ventricular rhythm	expired during recording*
6	m	maternal hypertension transverse lie abiallo placentae, caesarean section	1480	1	19 h 50 min	7.9	fixed rate marked bradycardia, high nodal beats, mild nodal rhythm	expired during recording*
7	m	normal	1810	8	23 h 44 min	8.1	fixed rate tachycardic rate marked bradycardia wandering pacemaker nodal rhythm, transitional A V block	expired later*
8	f	foetal asphyxia rapid delivery	1800	2	5 h 27 min	—	bradycardic rate marked bradycardia, nodal beats	recovered
9	f	delivery at home	1900	3-7	24 h 5 min	—	fixed rate, marked bradycardia	recovered
10	m	maternal uraemia, caesarean section	2450	5	6 h — min	—	fixed rate marked bradycardia nodal beats	expired after recording*

The autopsy finding in cases No. 1, 2, 3, 4, 5, 7 and 10 was pulmonary atelectasis with hyaline membranes in cases No. 1, 4 and 10. Additionally kernicterus was detected in case No. 3 and intraventricular haemorrhage in case No. 7.

ASPHYCTIC CASES

Results

In this material there were 10 premature infants, 6 boys and 4 girls, with asphyxia persisting during the ECG recording. The perinatal data and ECG findings of these cases are given in Table XI. The majority had an exceptional delivery small birth weight, and low Apgar score. Three of them died during the ECG recording, and only three recovered from asphyxia. One of the infants, case No. 8, had a neonatal hypoglycaemia, with a blood sugar of 13 mg per cent. 8 of them had a moderate to grave acidosis at the beginning of the recording. In 2 infants the acid-base balance was normal, and in 2 infants it was not determined. The mean rectal temperature was 34.6 (range 33.2—36.9°) at the beginning of the recording. 3 babies showed a moderate hyperpotassaemia, with serum potassium more than 7 mEq/l.

In the asphyctic group, neither means nor ranges of the basal heart rate differed from those of the healthy prematures. The peak heart rates did not exceed those of the healthy prematures. The tendency to occasional tachycardias of more than 170/min. was lower in the asphyctic prematures than in the newborn infants (Tables V VI). The asphyctic prematures showed a frequent predisposition to marked bradycardias of longer duration often associated with apnoeic attacks. No relation of heart rate alterations to other phenomena could be verified. The fixed heart rate pattern was present in 8 of the 10 asphyctic prematures (Fig. 10 Table XI). The fixation of cardiac rate was associated with progressive distress symptoms. No correlation could be demon-

strated between the initial rectal temperature and the corresponding basal heart rate.

True arrhythmias were rather common in asphyctic babies (Table VIII, Fig. 12, and Table XI). Only 2 infants (cases 3 and 9) were without any irregularities of cardiac action. Many of the infants had several kinds of arrhythmias following each other. Sinuatrial block appeared 6 times, without any symptoms, in the very immature baby No. 1. Wandering pacemaker occurred once in babies No. 2 and 7 in the manner shown in Fig. 14, but in these asphyctic infants, the gradual P wave inversion, and P-R time prolongation were associated with marked bradycardia during an apnoeic spell. Rhythm, originating from the A-V node, was found in 7 infants. In every case, nodal beats occurred during marked bradycardia. In 5 infants (cases 5, 6, 7, 8, and 10), there were sporadic high nodal beats. Long segments of high nodal rhythm occurred in cases 2, 4 and 7 and of mid-nodal rhythm in cases 5, 6 and 7. Infant No. 5 had, in addition, a short period of low nodal rhythm. Usually the nodal rhythm was reversible, but periods of nodal rhythm preceded ventricular rhythm terminally in the very asphyctic babies No. 2, 4 and 8 who died during the tape recording. Examples of arrhythmias in asphyctic infants are presented in Fig. 23. The ECG of the dying heart (case No. 4) is shown in Fig. 25. In all cases, the ventricular rhythm was followed by a complete asystole no ventricular fibrillation was observed.

In the asphyctic group the duration of the P wave ranged from 0.04 to 0.08 s that of the P-R interval ranged from 0.09 to 0.14 and the range of the QRS interval was 0.04—0.07 s.

Table XI. Data of the 10 asphyctic premature infants.

No.	Sex	Obstetric history	Birth weight (g)	Apgar score	Duration of tape recording	Serum K (mEq/l)	ECG findings	Response
1	f	normal	920	4	9 h — min	8	sinoatrial block	expired later*
2	m	breech delivery	1100	7	2 h 50 min	—	fixed rate marked bradycardia, wandering pacemaker nodal and ventricular rhythm	expired during recording*
3	m	normal	1250	8	19 h 22 min	5.7	fixed rate at the beginning initial 1° A V block	expired later*
4	m	breech delivery	1320	1	1 h 11 min	—	fixed rate marked bradycardia, nodal, and ventricular rhythm	expired during recording*
5	f	normal	1450	10	18 h 10 min	4.8	fixed rate, bradycardic rate marked bradycardia, nodal and ventricular rhythm	expired during recording*
6	m	maternal hypertension transverse lie, ablatio placentae caesarean section	1480	1	19 h 50 min	7.9	fixed rate marked bradycardia, high nodal beats, mild nodal rhythm	recovered
7	m	normal	1610	8	23 h 44 min	8.1	fixed rate tachycardic rate, marked bradycardia, wandering pacemaker nodal rhythms, transitional A V block	expired later*
8	f	fetal asphyxia rapid delivery	1800	2	5 h 27 min	—	bradycardic rate, marked bradycardia, nodal beats	recovered
9	f	delivery at home	1900	3-7	24 h 5 min	—	fixed rate marked bradycardia	recovered
10	m	maternal uraemia, caesarean section	2430	5	6 h — min	—	fixed rate marked bradycardia nodal beats	expired after recording*

The autopsy finding in cases No. 1, 2, 3, 4, 5, 7 and 10 was pulmonary atelectasis with hyaline membranes in cases No. 1, 4 and 10. Additionally kernicterus was detected in case No. 3 and intraventricular haemorrhage in case No. 7.

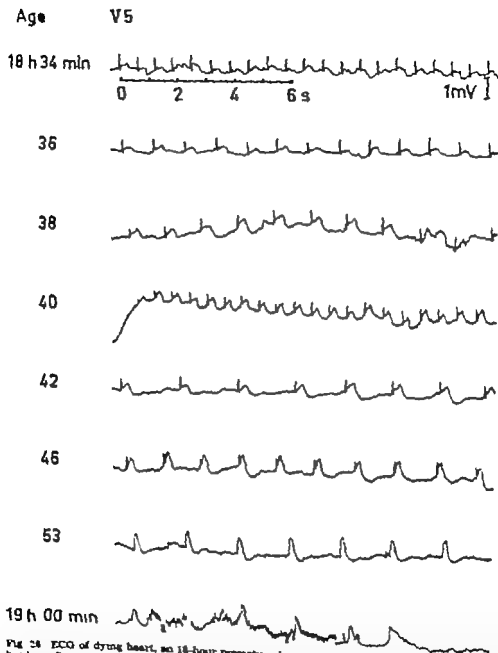


Fig 24 ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV I reproduction.

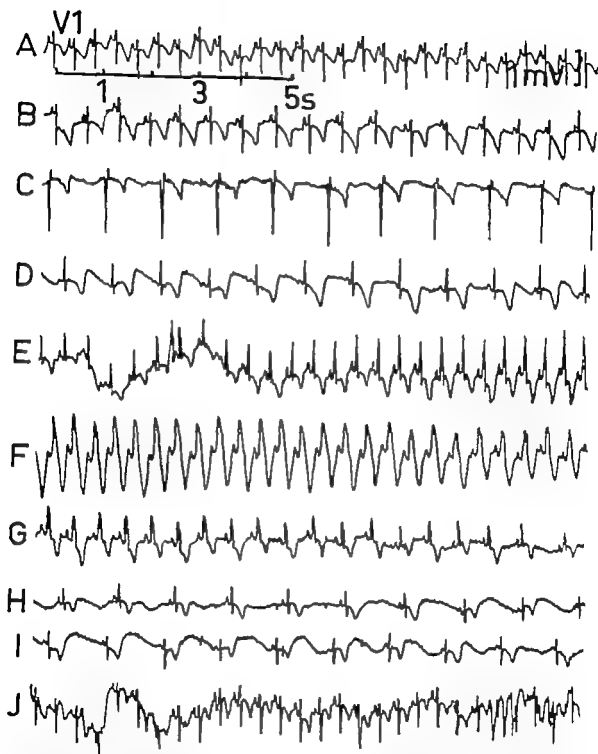


Fig. 25. Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7). A. normal pattern, B. bradycardia with occasional nodal escape beats, C. marked mid-nodal bradycardia, deformed ventricular depolarization, D. reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E-G transitional bizarre deformation of ventricular complex, H I. reappearance of bradycardia, occasional nodal escape beats, and J normalization of electric activation. MV 1 reproduction.

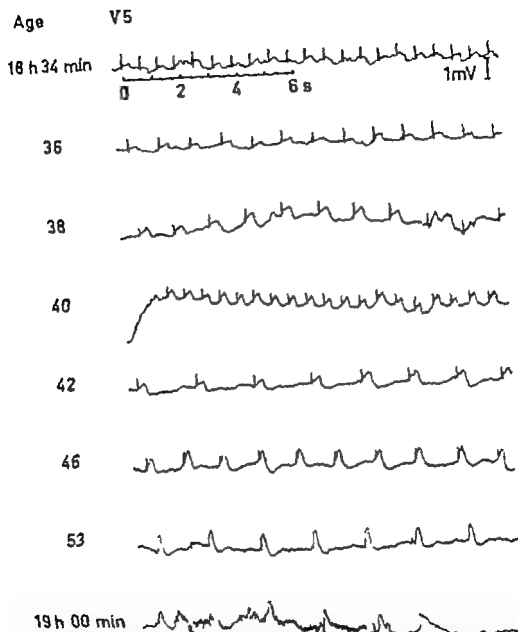


Fig 25 ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV 1 reproduction.

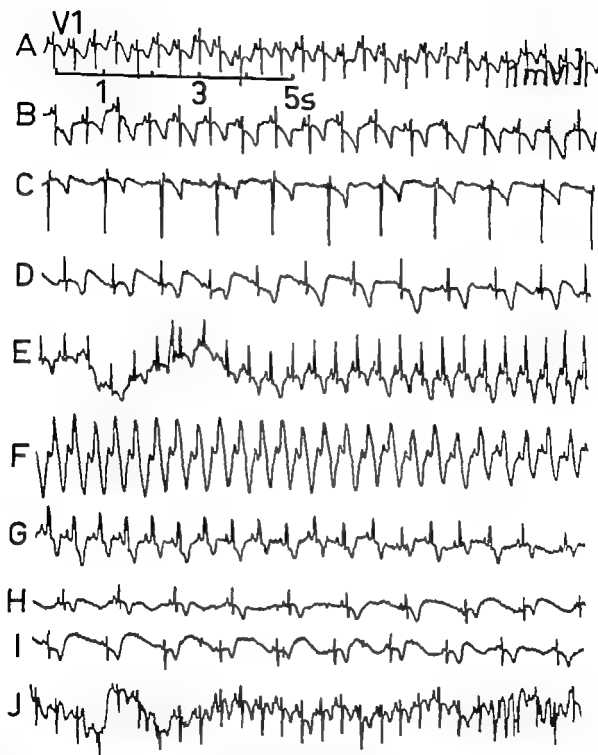


Fig. 23. Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7) A. normal pattern, B. bradycardia with occasional nodal escape beats, C. marked mild nodal bradycardia, deformed ventricular depolarization, D. reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E-G transitional bizarre deformation of ventricular complex, H I. reappearance of bradycardia, occasional nodal escape beats, and J normalization of electric activation. M V 1 reproduction.

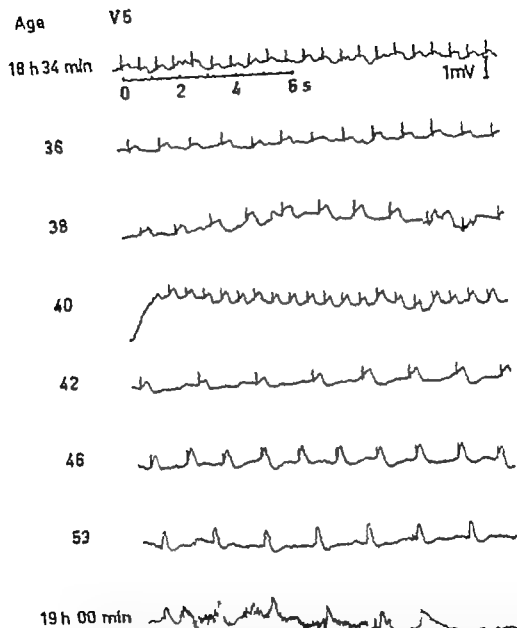


Fig. 26 ECG of dying heart, in 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV I reproduction.

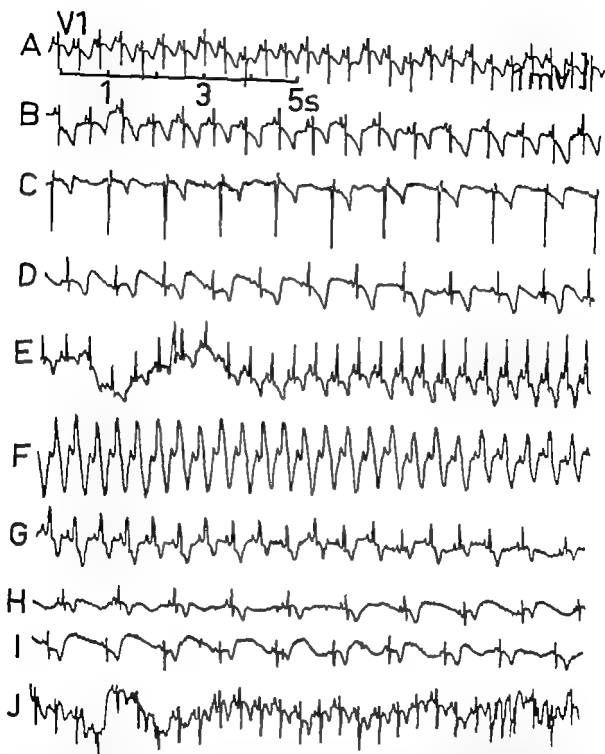


Fig. 25 Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7) A, normal pattern, B, bradycardia with occasional nodal escape beats, C, marked mid nodal bradycardia, deformed ventricular depolarization, D reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E-G transitional bizarre deformation of ventricular complex, H I, reappearance of bradycardia, occasional nodal escape beats, and J normalization of electric activation. MV 1 reproduction.

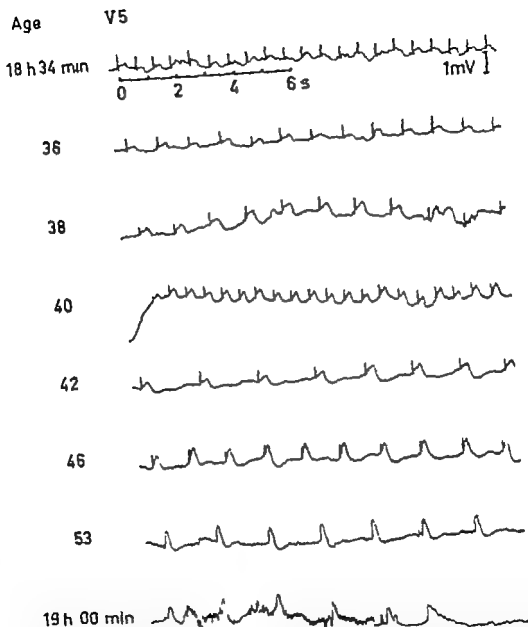


Fig. 24. ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MIV 1 reproduction.

The durations of the P wave and the P R interval were of the same magnitude, and they behaved in the same manner as the corresponding intervals of the healthy infants, when the nodal and ventricular rhythms were excluded. Only one infant, case No 3 had an initial P R interval of 0.14 s, but this decreased during the recording to 0.12 s. A severable 2:1 A V block appeared at the age of 24 hours in case No 7. An 0.01 s prolongation of QRS duration developed in cases 5 and 7. In the other asphyctic children the QRS duration decreased as in healthy prematures. The infants with a moderate hyperpotassaemia did not have prolonged P wave, P R and QRS interval durations.

All the Q-Tc values of the asphyctic prematures were within the range limits of the healthy prematures, the 2-hour and 24-hour values of which are given in Table IX. The mean values of the asphyctic group were initially the same as those of the healthy premature group. The initial Q-Tc values of the asphyctic prematures did not correlate with the rectal temperatures measured at the beginning of the recording or with the serum potassium concentrations. In 4 infants, cases 1, 5, 7 and 9 a Q-Tc prolongation of 0.005–0.01 s occurred during the observation time, but even these prolonged values were within the corresponding values of healthy prematures. No statistical comparisons were performed between the conduction time values of the asphyctic and healthy premature groups, because of the small number and unhomogenous recording time of the asphyctic group. For the same reason, the amplitudes of various deflections have not been compared with the values of healthy prematures. The

only clearly distinguishable feature of the amplitudes was a peaked P_{V1} in 6 infants. Grave alterations of the QRS axis were found in the recordings of the very asphyctic babies (Fig. 25 and 26). Left ventricular preponderance was initially present in cases 4, 6, and 7 and it began to develop in cases 1 and 5. The other infants had a typical neonatal right ventricular dominance.

Discussion

Fixation of heart rate, a typical heart rate pattern for asphyctic infants, has been earlier reported by Rudolph et al. [73] and Urbach et al. [93]. The disappearance of autonomic nervous control of the cardiac pacemaker resulting from depression of medullary centres in progressing asphyxia, has been regarded as an explanation of this phenomenon. The lack of sudden increases of heart rate during fixed rate, has also been observed by Urbach et al. but this pattern was interrupted by marked bradycardias, as in the study of Rudolph et al. and in the present material. Besides these bradycardias, rhythm and conduction disturbances have also been found in asphyctic babies by Ahvenainen & Landtman [1], Usher [94] and Rudolph et al. [73]. Although abrupt bradycardias are to be detected in full term and healthy premature infants, according to the reports of Morgan et al. [53], Morgan & Guntheroth [57] and Urbach et al. [93] they seem, according to the present results, to be more profuse and of longer duration, in asphyctic infants during the first day of life.

Of the irregularities of cardiac action, extrasystoles and WPW syndrome, have been mentioned by Ahvenainen &

Landtman [1], ventricular rhythm and extrasystoles by Åkerén [114] and Kötigen & Feyerabend [44] and conduction defects, or wandering pacemaker by Rudolph et al. [73]. Wandering pacemakers, nodal and ventricular rhythms, were found in the present series, but grave irregularities like ventricular rhythm appeared only in terminal asphyxia. Delayed atrio-ventricular conduction, II—III degree A V blocks, prolongation of QRS duration, and bundle branch blocks have been described in asphyctic infants [14, 44, 60, 94]. Koivikko described a total A V block appearing during an experimental combined acidosis resulting from asphyxia in a newly born lamb [43]. In the present study there were P R interval and QRS durations, equal to the prolonged ones in the articles mentioned above, but they were within the limits of corresponding values of the normal series. The P R intervals were quite the same in asphyctic and normal newborn, and only slightly prolonged QRS intervals were found by Ringel in the asphyctic group [70]. The conduction times have been reported, by Usher to be prolonged by concentrations of serum potassium over 5.0 mEq/l [94]. Only a transitional A V block was presented in one of the 3 infants with hyperpotassaemia of more than this value in the present series. However it must be remembered, that relationships between the intracellular and extracellular potassium contents cause ECG changes, and we have no information about the intracellular levels.

The etiology of these heart rate alterations has not been determined. Most of the cases of Kötigen & Feyerabend had intracranial haemorrhages, and it was thought that the electrocardiographic changes could be of cen-

tral origin [44]. Also, the material of Ahvenainen & Landtman included 32 patients (25 per cent) with intracranial haemorrhages, but only 4 of them had electrocardiographic changes [1]. In the present asphyctic group, there was only one (case No. 7) who had intraventricular haemorrhage, found at autopsy several days after the recording. Phillips et al. [80] were able to produce marked bradycardias and nodal beats, by vagal stimulation in normal prematures [85]. The present results, and the reports of Walsh (108, 109) on the effect of cord clamping, indicate the role of volume load as an etiological factor in prolonged conduction in healthy newborns. The central blood volume has been reported by Koivikko to increase during asphyxia in newborn lambs [43]. Although the etiology of rhythm and conduction disturbances in general is rather obscure, it would seem evident, that increased vagal tone, or increased sensitivity to vagal tone, may be responsible for these ECG alterations in asphyxia.

Peaked and notched P waves in right precordial chest leads, have been reported in asphyxiated children by Sutin et al. [88, 89] broadening and flattening of the P wave by Usher [94] but according to the article of Keith et al. these do not differ from those of normal newborn infants [41]. The asphyctic babies had higher P waves in the investigation of Ringel, and the amplitude was found to increase in a hypoxia test [70]. Peaked right precordial P waves appeared in the present asphyctic group, but no changes in their form could be demonstrated with the tape recording technique, except those found in association with wandering pacemakers and nodal rhythms. The disappearance of the P

wave mentioned by Usher [94] and Sutin et al. [89] was found in 2 infants (No 6 and 7) and was considered as a mid-nodal rhythm.

Left ventricular preponderance was an electrocardiographic feature of asphyctic newborns in the study of Usher [94]. In the investigation of Keith et al. low pulmonary vascular resistance and open ductus arteriosus were associated with this pattern, while asphyctic infants with right ventricular dominance had high pulmonary resistance and open ductus, the prognosis being better in the latter cases [41]. The same observation was also made by Sutin et al. [89]. Left ventricular dominance began to develop in 2 infants of the present series, both of whom died, and this pattern was initially present in 3 additional cases, 2 of whom also died. According to Keith et al. this pattern disappears after the ductus closes. Decreasing QRS amplitudes were observed only in terminal asphyxia in the present study.

S-T deviations and pathological flat T waves were the main findings in

asphyctic babies in the study of Ahvenainen & Landtman [1]. Ringel succeeded in producing the T wave flattening by the hypoxia test in asphyctic newborns [70]. Peaked T waves and prolongation of Q-T interval were asphyctic abnormalities in the material of Usher [94]. The latter finding was also mentioned by Keith et al., and prolongation of the Q-T interval was also found to develop in the present material. The upright, right precordial T waves remained longer in premature, and asphyctic infants in the same study [41]. No uniform alterations of the T wave were observed in the present material. Minimal morphologic changes were detected in the coronary arteries of some asphyctic babies with abnormalities in the ECG by Ahvenainen & Landtman [1]. These authors, however together with Ringel [70], Usher [94] and Keith et al. [41] believe that these changes of ventricular repolarization, result from metabolic and electrolyte alterations, caused by asphyxia in the myocardial cells.

CONCLUDING DISCUSSION

When the electrocardiogram of new born infants is studied by means of the long-term recording technique, the main interest will be focused on the areas which are to be reached only by continuous recording, and in which this technique will be expected to be superior to the conventional ECG. These areas are heart rate alterations, incidence of arrhythmias, alterations of conduction times, and alterations of the voltages of different deflections of the ECG. Because of the alteration nature of this research, the basal pattern of the function must be established for comparison. To get information about the reliability of the method it must be assured that these basal patterns are in agreement with the previous results of the same area. Finally it must be decided how the new features of the neonatal ECG accord with the modern conception of the cardiac physiology of the newborn infant.

According to the present results, the heart rate behaved just as it has been found to behave in the earlier long term electrocardiographic and cardiographic studies [16, 48, 92, 99, 100]. The minimal and maximal heart rate values deviate more from the basal level than previously expected. However the minimal phase variation of the pacemaker activity of the sinoatrial node persists in the maximal heart rates, and this is hard to demonstrate in conventional ECG. Fixation of heart rate is a warning sign which may be present in healthy premature, but is a typical finding in asphyctic infants.

The gradual changes of various electrocardiographic intervals, demonstrated in the present investigation, are

in agreement with the results obtained as momentary samples by conventional ECG but the timing of these changes during the first day of life has been determined more exactly in this study. As the basal heart rate tends to be minimal at the age of 3-6 hours, the physical activity has also been reported to be minimal during this time [16]. It is, however interesting that infants with a birth weight of 2000-3500 g have a lower post-delivery dip of basal heart rate than infants with lower and higher birth weights, and that this difference remained up to 18 hours of age in the present material. During the first 6 hours a clear decrease of conduction times appears, and this shortening continues in the case of the P-R interval, up to the age of 14 hours. The present results confirm the observations, and support the hypothesis of Walsh [103] that the same regulating factors will be responsible for these changes of P wave, P-R interval, and QRS interval durations. When heart rate alterations, changes in these conduction times, and the effect on them of the moment of clamping of the umbilical cord are all considered, the obvious explanation for these changes may be increase in vagal tone, post partum, as a result of volume load of the heart, but this may also have a direct effect on the ECG, as has been discussed earlier in the articles of Walsh [102, 103, 109]. The behaviour of Q-Tc interval is quite different from those of the other intervals. The Q-Tc changes cannot be explained by changes of electrolytes and body temperatures, according to the information obtained in the present study.

A contrary result to those of Morgan *et al.* [35]. Morgan & Guntheroth

wave mentioned by Usher [94] and Sutlin et al. [89] was found in 2 infants (No 6 and 7), and was considered as a mid nodal rhythm.

Left ventricular preponderance was an electrocardiographic feature of asphyctic newborns in the study of Usher [94]. In the investigation of Keith et al. low pulmonary vascular resistance and open ductus arteriosus were associated with this pattern, while asphyctic infants with right ventricular dominance had high pulmonary resistance and open ductus, the prognosis being better in the latter cases [41]. The same observation was also made by Sutlin et al. [89]. Left ventricular dominance began to develop in 2 infants of the present series, both of whom died, and this pattern was initially present in 3 additional cases, 2 of whom also died. According to Keith et al. this pattern disappears after the ductus closes. Decreasing QRS amplitudes were observed only in terminal asphyxia in the present study.

S-T deviations and pathological flat T waves were the main findings in

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SUMMARY

The first section of the present investigation consisted of a description of the ECG tape recording devices of Holter—Avionics, and some additional instruments modified and calibrated for examination of newborn infants. This part also included a comparative study of the signal reproduction in a conventional electrocardiograph, and in different tape recording instruments, the recordings of three chest leads, V1 V3, and V5 having been performed in a material of 30 full-term newborn infants. The results indicated that the time quantities in all the reproductions were equal. No significant differences could be demonstrated between the voltages of the P and T wave reproductions of Electrocardioscanner and those of both writing-out methods and conventional ECG. A marked attenuation of the voltage of the R wave, and particularly that of the S wave, appeared to be produced by the tape recording apparatuses when compared with conventional ECG. This distortion was mainly increased in both writing-out methods. The relationship between the Electrocardioscanner reproduction and the conventional recording of the R and S wave amplitudes in the three chest leads was presented (Fig. 5). An extra upright deflection, post-S spike, was rather frequently found at the end of the QRS complex in the tape recordings, and this deflection was considered to be

an artifact caused by the equipment. The ability of the tape recording instruments to repeat S-T deviations proved to be unreliable, but the incidence of these deviations in the material was insufficient for far reaching conclusions. This was also the case with the incidence of the U wave in the material.

In the second section, electrocardiographic changes were studied with long-term recordings in 50 full term, 30 healthy premature, and 10 asphyctic premature newborn infants during the first day of life. The effect of early versus late clamping of the umbilical cord was studied by clamping the cord immediately after delivery in 10 infants of the full-term group. The ECG findings were compared with the information from the obstetric history and clinical observations of the infants, as well as the serum potassium (66 determinations) and calcium (30 determinations) concentrations of the material. The total durations of the recordings were 1248 hours in the full term group, 614 hours in the healthy prematures, and 129 hours in the asphyctic prematures.

The most important findings in the long term recordings were

- 1) The mean basal heart rate behaved equally in all the three groups, having a minimum level at the age of 3-6 hours (Fig. 8). The infants with a birth

[57] and Church et al [9] is found in the present study in which cardiac arrhythmias appear to be most common in infants with a birth weight of more than 3500 g (up to 4850 g). However the recording times were shorter in the premature group which may have affected the results. In spite of this, it can be stated that both bradycardias and cardiac arrhythmias also appear in full term infants in the first day of life. Both healthy and especially asphyctic infants, seem to be disposed to marked sinus depression evidently of vagal origin, and in these situations a compensatory capture of the pacemaker activity of the lower parts of the heart, mostly of the A-V nodus, takes place. In the light of the articles of Phillips et al. [66] and Manning & Wallace [51] and the present results, the role of central stimulation and the balance of the autonomic nervous system in the regulation of cardiovascular function, call for further investigation.

The unique electrocardiographic behaviour of the highest birth weight group with a higher heart rate, high incidence of arrhythmias, and shorter Q-Tc interval, is worth noting, but the explanation for this remains open.

The present voltage patterns are peculiar to the recording technique used and can be compared with conventional ECG studies by the aid of the results described in section I of this investigation. However the changes in the amplitudes of various deflections, although the most unreliable of the present results, are in agreement with the previous conventional ECG recordings. Thus, they reflect a decrease in the neonatal right ventricular preponderance even during the first hours, and, in the group of prematures, an additional decrease of the left ventricular forces. These changes have been generally attributed to alterations in pulmonary vascular resistance, and to the closure of the ductus arteriosus.

waves and R/S ratios in the three chest leads indicated diminution of the neonatal right ventricular dominance as early as the first day of life in both healthy groups. There was also a diminution of left ventricular forces in the healthy prematures (Fig. 21). The amplitudes of the II and III waves could be compared with the results of conventional ECG only by means of the diagram in Fig 5

8) The T waves in VI and V3 leads were generally positive during the observation time in the full term group. The T_{V3} waves were mostly inverted after 3 hours of age in the full-term (Fig. 23). T waves of the healthy prematures were of lower amplitude and

they generally became inverted in V3 lead after 8 hours.

The results were compared with earlier ECG studies, and discussed in the light of the present information in neonatal cardiovascular physiology. It could be concluded that valuable data can be obtained by continuous ECG tape recording of the heart action of small infants. The results gave an impression of functional nervous control of the neonatal cardiac action, the maturity of which is possibly related to the maturity of the infant, and this should be considered when the therapy of the disorders of neonatal cardiovascular adaptation is planned.

weight of 2000—3500 g had significantly lower mean basal heart rate levels than the infants weighing less or more (Fig 9). The level of the basal heart rate was mainly 100—125/min, but there was a tachycardic group of 14 per cent of the whole material, with a basal rate always more than 125/min, and the majority of these cases were premature. No relationship was found between the basal rate level and sex, number of deliveries of the mother, maternal hypertension, moment of the cord clamping, Apgar score, or serum calcium or potassium concentrations. A very low positive correlation could be established between the initial basal heart rate and the rectal temperature of the infant. There was a significant difference between the mean basal heart rate levels one hour before and after the first feeding in the full term group.

2) The full term infants showed a more prominent and earlier developing tendency to tachycardic phases than the healthy premature, and the peak heart rate values of the asphyctic premature never exceeded those of the healthy groups (Fig 8). The maximal cardiac frequency was 260/min, and the maximal duration of a tachycardia with a rate of more than 170/min was 80 min in the whole material. Occasional shortenings of P-R interval and changes of T wave voltage appeared in connection with the tachycardias.

3) Abrupt bradycardias with a frequency lower than 90/min occurred quite equally in both full term and healthy premature infants, but the asphyctic group expressed a particular tendency to more marked and longer bradycardias than the healthy group (Fig 8).

4) A minimal phasic variation of the heart rate was always present in the

full term, and mostly in the premature group even during maximal tachycardias. Fixation of heart rate was occasionally seen in the healthy premature, but this pattern was especially typical for babies with progressive asphyxia.

5) Cardiac arrhythmias, mostly asymptomatic, were rather common in all groups (Fig 12 Table VII). Their relative incidence in the healthy infants proved to be highest in the full term weighing more than 3500 g. More arrhythmias were found in healthy females than in healthy males. Marked sinus depression, followed by compensatory nodal and ventricular rhythms, was common in asphyctic infants. The cardiac action terminated with ventricular asystole during the recording of 3 infants.

6) A gradual shortening in the durations of the P wave, P-R interval, and QRS interval occurred during the first hours of life, this being most pronounced during the first 6—7 hours in the healthy infants (Fig 17). The P-R values of the group with the early clamped umbilical cords were significantly lower than those of the late clamped group, during the first 4 hours of life. The behaviour of the Q-Tc interval was different from those of the other conduction times. From the 6th hour of life the Q-Tc values of the healthy premature were significantly higher than those of the full term, and the group weighing over 3500 g had the lowest Q-Tc values (Fig 18). The 2-hour and 24-hour values of these intervals are presented in Table IX. A tendency to prolonged Q-Tc intervals was found in the asphyctic group.

7) No uniform, gradual alterations of P wave voltage were detected. The gradual alterations of the R and S

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ACKNOWLEDGEMENTS

I am deeply grateful to my chief Professor Tuomas Peltonen, M.D., Head of the Children's Hospital, University of Turku, and to Associate Professor Leo Hirvonen, M.D. Head of the Cardio-respiratory Research Unit, University of Turku. They aroused my interest in paediatric cardiology and their extensive knowledge of clinical and experimental cardio-pulmonary neonatology has been of great help to me throughout my studies.

My thanks are also due to Professor Kaarlo Harttala, M.D., Head of the Department of Physiology in which the Cardiorespiratory Unit forms a section.

I am very grateful to Professor Fritz Graser, M.D., my chief in Städtische Kinderklinik Wiesbaden, West-Germany for his invaluable advice and stimulating interest in my work.

I wish to express my gratitude to Dr Matti Takala, M.D. Head of the Municipal Maternity Hospital of Turku, and Dr Eila Maija Harrela, M.D., Head of the Obstetric Department of the District Hospital of Loimaa, and the members of their staffs. I am also grateful to the staff of the neonatal department of the Children's Hospital, without whose continual assistance my work would have been confronted by many practical difficulties.

I am indebted to Docent Heikki Frick, M.D. Head of the Cardiology Laboratory Mellahti Clinics, University Central Hospital of Helsinki, for allowing

me to use the equipment of this laboratory for comparative analysis of my recordings.

My sincere thanks are due to my very good friends Mr Pekka Mäkelä, M.A., and Mr Timo Ahman, electronic engineer for their valuable technical assistance.

I wish to thank Mr Matti Grönroos, B.A., Institute of Applied Mathematics, University of Turku, for programming the data processing and checking the statistical aspects of my study. I also thank Mrs. Irma Salminen, R.N. for her assistance in preparing my results for data processing.

Mrs. Aili Ryyänen, M.A., librarian of the Medical Library University of Turku, and her staff helped in the collection of the literature, for which I am very grateful.

I am very much obliged to Mr Colin Black, B.A., Language Institute of Turku, and Mr Malcolm Cheyne, University of Dundee, Scotland, for their revision of the manuscript.

I extend my thanks to Mrs. Vuokko Uusitalo and Miss Hellin Aaltonen for their secretarial assistance.

This work was supported by grant of the Finnish Heart Foundation, and grants awarded by the State Commission for Medical Sciences, and Sigrid Jusélius Foundation to the Cardiorespiratory Research Unit.

Turku, September 1989

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BY MAIJA LIISA KOSKI



ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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Introduction

The psychological problems of diabetic children have attracted the attention of many well known diabetologists and child psychiatrists. Several articles have touched upon the possible etiological relationship between emotional disturbance and childhood diabetes (18, 143) Other authors have reported that emotional factors in the child's life seem to exercise an influence on the course of the diabetes (64, 127) The diabetes itself creates many special problems for the child and his family. There is an awareness of being different from other children. Diabetic children experience daily frustrations centered around eating and insulin injections. Authors have been aware that the patient's management

of diabetic routines may become an avenue for emotional expression (91, 129)

My interest in the study of the psychiatric aspects of childhood diabetes began in 1962, when, as a consultant child psychiatrist for the Children Hospital of the University of Turku, many problems of diabetic children and their parents came up at the meetings with pediatricians and nurses. In spite of the extensive attention given to childhood diabetes in the medical literature, the interplay between the emotional experience of the child and his family and the controllability of the child illness seemed to be in need of further study and discussion.

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The purpose of the present investigation

The aim of the present study is twofold it tries to find answers to the following questions:

1. How does the family and especially the mother react to the discovery of diabetes in her child? Subsidiary to this what more lasting reactions and attitudes develop within the family and especially in the mother as time goes on? In the present study these lasting attitudes are called coping processes.

2. How does the child react to the discovery of diabetes in himself? Subsidiary to this, how well adjusted are diabetic children after at least one year' duration of the illness?

In the final part of the study an attempt is made to find possible correlations between various coping processes adopted by both mother and child and the effect of these on diabetic control.

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Survey of the Literature

Psychosomatic research on diabetes mellitus in adults

Interest in the relationship of diabetes mellitus to emotional disturbances dates back to the seventeenth century. Thomas Willis described the sweet urine of the diabetic and thought the disease was due to "long sorrow." Clinical observations of the relationship between diabetes and mental illness were frequently recorded in the late nineteenth century. Savage wrote that "In insanity proper diabetes was rare, but when these two illnesses, which have familiar trends, coincided, the mental illness was of depressive type." Mandley also pointed out that nearly all (diabetic) patients were melancholic (124).

Psychic trauma as a precipitating factor in diabetes

The relationship of diabetes to emotional loss as first described by Pike in 1923 in a report of a patient who developed diabetes after having lost his wife to another man (108). The role of emotional deprivation was further supported by the observations of Neilson (102).

The opposite view was taken by Menninger in the twenties-thirties, who found that psychic trauma had been an important precipitating factor in only two of his 93 cases of uncomphorated diabetes (94). Damber and co-workers, in a comparative study found preceding emotional trauma in the history of diabetic patients less frequently than in the history of cardiac and fracture patients, and considered that a long period of stress was a more frequent occurrence in the life of diabetics. In the diabetic and cardiovascular groups they found that anxiety was prominent factor (34).

The essential feature, according to Daniels in 1939 was not the trauma, although this may play an important role, but the type of conflict measured in terms of anxiety and tension. Another important factor to bear in mind, according to Daniels, was that repressed emotional tension seems to have greater opportunity for discharge through the autonomic nervous system (25). This explains much of the seeming contradiction in the effect of transitory emotional

upsets on sugar metabolism, which so confused Joslin as to lead him to rule out the whole phenomenon as of little importance (73).

Daniels, in his review of the experimental, general medical, and psychiatric literature of the preceding five years, stated that in general medical writings there were relatively few references to the existence of emotional factors. Further when such references were made there was a tendency to minimize their importance. On the other hand the few papers contributed by clinicians trained in psychological medicine did reveal an awakened interest in, and a new approach to this problem. Observers trained in psychiatric methods could clearly demonstrate that neurotic manifestations were frequent in cases of diabetes mellitus (25). Menninger listed nine of a series of thirty cases studied by him as psychoneurotic (94).

Daniels stated that any ultimate understanding of the psychopathology associated with diabetes must develop from exhaustive and painstaking study of cases with parallel observations on accompanying physiological changes (25).

Experience gained in World War II produced doubts about the significance of emotional stress as precipitating influence in diabetes (50). Many of the older references relied primarily on gross observations of very sick patients in a hospital setting. In addition, the temporal relationship between the metabolic disease and the emotional disturbance was often obscure (124).

Hinkle and Wolf measured changes in blood sugar and blood ketones under stress and concluded that an inappropriate metabolic adaptive mechanism is activated by stressful life situations which represent a loss of affection and security. These authors concluded that the metabolic derangement of diabetes is merely an accentuation of the normal response to carbohydrate starvation triggered by an emotionally threatening life situation (60). More recently Kaplan and Kaplan have reported that glycosuria is diminished in depressive diabetics treated with the antidepressant imipramine hydrochloride. When the drug was discontinued the glycosuria returned to premedication levels (75).

In the nineteen fifties Goldner stated that the diabetic patient reacts to severe stress with aggravation of his disease often to the extent of ketoacidosis or coma. Such stressful experiences may be intermittent diseases or severe trauma as well as sudden and severe emotional disturbances. Even the nondiabetic, under such conditions, may not infrequently develop similar though less marked metabolic changes characterized by such features as hyperglycemia, glycosuria, and ketonuria. This phenomenon seems to represent part of the nonspecific stress reaction. It is exaggerated in the diabetic only because it is here superimposed upon a previously impaired carbohydrate metabolism. The recognition that manifest diabetes mellitus can be aggravated by extrapancreatic functional and environmental factors leads of necessity to questioning whether these factors may also be operative in the causation of the disease. From the theoretical point of view one would expect that a disease-aggravating factor when severe enough may become a disease-precipitating or even -causing factor (51).

In the nineteen-sixties Slawson and co-workers evaluated 23 newly diagnosed adult diabetics psychiatrically and obtained the following results:

- 1) fourteen gave a history of definite object loss
- 2) a further six gave evidence of a loss that could be reasonably inferred
- 3) ten presented findings of unresolved grief
- 4) fourteen were considered to be living in an emotionally deprived environment and
- 5) seven were found to be clinically depressed.

They suggested that (adult) diabetic patients may be particularly prone to a specific stress and that their response to emotional deprivation may be a non-adaptive shift to the type of metabolism characteristic of starvation (124).

Danowski discussed emotional stress as a cause of diabetes mellitus as follows: "Obviously somewhere between the clearly nondiabetic normal group and the clearly diabetic group there must be a group of people who are developing diabetes mellitus. In such individuals a stress which would produce only transient impairment of carbohydrate metabolism in members of the clearly nondiabetic group could theoretically produce permanent diabetes mellitus where none existed previously. The crux of the problem is analogous to the question: How many straws are needed to break a camel's back? (28)

Characteristic personality structure in diabetes

In the nineteen-thirties several authors made attempts to describe a personality structure characteristic for diabetes.

Menninger described the composite status of a diabetic, which, though suggestive, was on the whole confusing. This may be accounted for by the fact that ten diabetic conditions were diagnosed in his series of patients. His observations on the effect of diabetes on intellectual functions are of 1) Diminished alertness and awareness of the environment were reported as characteristic though the individual was sometimes much too alert to his own condition and events directly affecting himself. Memory disorders, mindedness and delayed psychic responses were more pronounced in diabetics than in non-diabetic individuals. (94)

Miles and Root in their psychological study on diabetics found a decrement of 15 per cent or more in the performance of memory attention tasks on testing 39 patients who had hyperglycemia and glycosuria as compared with controls. With treatment they found a rapid improvement in psychological status approach but not quite attaining the normal level. In 17 long-standing treated cases of diabetes they found that the accuracy and speed of movements 20 per cent below normal (98).

Dashiell reported a case in which, in hypoglycemia the patient showed increased deficiencies in the same rather than opposite directions (29).

The theory that a specific personality type incurs a specific psychosomatic disease is Dunbar's. Dunbar and co-workers described a personality profile of the diabetic patient pointing out that from early childhood and before the onset of disease diabetic patients have difficulties in making the adjustment which is necessary before one progresses from the infantile state to the more mature independent one; consequently such individuals vacillate from attitude to the other, the impulse of independence being asserted mainly in words and only very little in action. Paralleling this difficulty is an inability to attain mature psychosexual development (34). Dunbar's theory is now only of historical interest because there is considerable evidence to show that it is an oversimplification. However, the impact of her

early statements is attested by the frequency with which they are denied. Many later studies of psychosomatic diseases include the statement that no specific personality type was found." Thus for instance, Bruch stated that although investigations of adult diabetics have made with the object of uncovering characteristic and predisposing traits, so far no uniform picture has emerged (18)

To be seen of diabetes

Messinger reviewing the literature, came to the conclusion that there was a group of toxic cases, to be regarded as diabetic psychoses, but that these represented only a small percentage of the number of cases in which diabetes and mental disease were associated. He cited three such cases from his own series. (94)

Benedek on searching the literature, found only nine cases, including Messinger three, in which he felt it was justifiable to consider a relationship between diabetes and abnormal psychia states. He concluded that such toxic mental states were independent of personality traits or inherent familial tendencies and attributed them to hyperglycemia. (13) Caution is necessary however before it is concluded that such toxic effects are the primary factors determining the mental picture, as is illustrated in one of the cases reported by Katz (78)

Harris, after a careful study of experimental data showing the ability of the brain to utilize carbohydrate as its main source of energy concluded that in mild or moderately severe diabetes there is little likelihood of any disturbance of brain function, with mental symptoms due to the hyperglycemia alone. In severe diabetes, acetone, keto-acids and beta-hydroxybutyric acid appear. There is disturbance of the electrolyte equilibrium with a loss of bases from the body. He concluded that only in severe diabetes will mental symptoms be produced by the toxic effects of the disease and then only in the last stages. He further stated that similarities exist between the mental aberrations seen in psychoses and manifestations in hypoglycemia, whereas such phenomena are seldom seen in hyperglycemia. (55)

Anger and excitement produced by the disease

In the literature in the nineteen-thirties, depression was found to be one of the most frequent mental symptoms of diabetes mellitus.

Daniel found that depression was an important complication in ten cases of the twenty-three diabetic admissions studied. In five cases the depression was reactive to the loss of a loved object prior to the onset of diabetes. Daniels suggested that, when possible a distinction should be drawn between depression of primary nature, which might not be related to the diabetes, and depression secondary to the diabetes. The individual's knowledge that he is suffering from an incurable disease which, on account of the care necessary in treatment, sets him apart from the rest of his fellows in many cases explains his reaction. Much of the hypochondriac self-observation which often accompanies such depressions can be explained in the same way. Because it is so natural, however to conclude that such a patient is apart from his condition, it is possible to miss more fundamental neurotic reactions which may play more primary role. (23)

Beardwood reported two cases of attempted suicide with insulin. One of them was a diabetic woman who had taken 400 units of insulin just prior to admission to hospital. (4)

In the nineteen-forties, Benedek described the traumatic effect of the diagnosis of diabetes mellitus upon the patient, an effect which is believed to be deeper than the anxiety induced by other chronic diseases. The diabetic patient may develop a habit of dealing with every external and internal situation in terms of food and of his diabetes. Thus various types of character reaction may be observed in diabetic patients. Those whose ego-structure is strong react with extreme compulsiveness in regard to diet while those whose ego-structure is weak respond with overeating and with provocative attitudes in regard to diet. Benedek suggests that the processes secondary to the diabetes may become an integral part of the personality so that we can speak of a superstructure of the diabetic individual. The individual differences in the adaptation to diabetes probably mainly depend on the integrative capacity of the ego. (9)

Minsky points out that the onset of diabetes mellitus may produce profound psychological changes in patients, as well as in various other members of the family. Thus their pride may be hurt, their fears and feelings of inadequacy may become intensified, and their aggressive feelings may be aroused, so that they may show great emotional reaction to the onset of the diabetes. (99)

In the nineteen-fifties Goldner stated that the diabetic patient reacts to severe stress with aggravation of his disease often to the extent of ketonacidosis or coma. Such stressful experiences may be intercurrent diseases or severe trauma as well as sudden and severe emotional disturbances. Even the nondiabetic under such conditions may not infrequently develop similar though less marked metabolic changes characterized by such features as hyperglycemia, glycosuria and ketonuria. This phenomenon seems to represent part of the nonspecific stress reaction. It is exaggerated in the diabetic only because it is here superimposed upon a previously impaired carbohydrate metabolism. The recognition that manifest diabetes mellitus can be aggravated by extrapancreatic functional and environmental factors leads of necessity to questioning whether these factors may also be operative in the causation of the disease. From the theoretical point of view one would expect that a disease-aggravating factor when severe enough may become a disease precipitating or even -causing factor (31).

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Psychosomatic research on diabetes mellitus in children

According to Keeler more, perhaps, has been written about diabetes from the psychological standpoint than about any other childhood disease, excluding those considered psychosomatic. The major concerns have been, 1) the relationship between the emotions and the medical course of the diabetes and 2) emotional reactions to the management of the illness. (80)

Dietary restrictions and the daily injections of insulin are liable to cause many problems. The mother relationship with her child is strained by prohibitions of certain foods and infliction of pain at the injection. Children are apt to attribute the illness to eating too many sweets and so may feel guilty. Similarly if the sugar metabolism gets out of control, both the parents and the child may feel guilty.

In two of the cases studied by Daniels, diabetes occurred in childhood at a time when an infantile neurosis appeared to be acute. The factors precipitating the neurosis may also conceivably have precipitated the diabetes. That there actually was a link between the neurosis and the onset of diabetes certainly could not be proved. (24)

Fischer and Dolger described guiltiness, insecurity and dependency as characteristics of young diabetic patients. (44) Benedek suggested that no chronic disease of childhood produces more anxiety in the mother than diabetes mellitus. (9) On the other hand, in Korach's view virtually all parents of physically handicapped children have feelings of guilt and of personal responsibility for the handicap. (82)

Bruch stated that the need for adequate metabolic treatment of the diabetic condition so as to insure more normal growth and freedom from physical ill-health had long stood in the foreground of medical thinking, but it was only in the nineteen-thirties that the psychological problems of diabetic children had gained attention. Her own observations were made on 37 diabetic children. As was the fashion in psychosomatic medicine at that time she was concerned with specific personality structure in diabetic children and psychological characteristics of the family setting in which diabetes had developed. One focus of Bruch's inquiry was upon factors which may have been of traumatic significance in the development of diabetes. There were disturbances in family relationships, such as divorce, birth of

a sibling, death, boarding out with relatives, etc., in 10 of the 37 cases. Only in one case had the family connected this event with the onset of diabetes while in another case a relationship was later suspected between the onset of diabetes and the child's separation from the father who had played an affectionate role in the life of his son.

As Bruch remarked, if the disease had existed for several years it is difficult if not impossible, to differentiate between the pre-existing psychologic picture and the influence of the diabetic regimen on the family. She differentiated three main ways in which the mothers reacted towards the diabetic regimen.

1 *A tolerant and relaxed acceptance* of the responsibility. This attitude seemed to produce fairly satisfactory regulation and adjustment in the children. While it may be recognized as the most desirable attitude, it was the least frequent in Bruch's cases.

2 *A perfectionistic overcontrol*. With this attitude, all tasks become expressions of the mother's absolute need to do the right thing. Here the basic attitude toward the child is aggressive and subduing. Yet this overcontrol of the child was characteristically associated with satisfactory regulation of the diabetes, and these families were rated as good and co-operative. Frequently behavior difficulties occurred in other fields, such as eating, poor school-work or sudden rebelliousness.

3 *Erratic or persistently poor co-operation* regarding the medical regimen. Such an attitude, of course produced poor control, with marked fluctuation in the degree of regulation. Satisfactory regulation was always the exception. Despite these consequences, this attitude was the most frequent. (18)

Since the nineteen-forties many authors have stressed the psychological problems of young diabetics.

Mason called attention to the existence of diabetes as the background illness for suicidal behavior in three disturbed adolescent girls. (92)

Katz mentioned the greater incidence of behavior problems in diabetic than in nondiabetic children. (77)

Stearns pointed out that many young diabetics exhibit signs of unreasonable behavior which can be interpreted as essentially self-destructive. Such behavior was most frequently exhibited when major life adjustments had to be made

In the nineteen-fifties Smith and Brown attempted to evaluate the responses of twenty five adult diabetics to their illness. The group was found to present two different types of responses a group of 19 with obesity and minimal concern over their condition and a group of 6 patients with marked concern about their long standing neurotic symptoms. It was felt that the lack of concern observed in the 19 obese diabetics was an important factor in their not keeping to the dietary regimen (125)

Beaser points out that the diabetics basic difficulty adhering to his diet is psychological rather than physiological. Also he adds even superficial psychiatric observation of diabetic patients reveals that many kinds of environmental and intra psychic factors are important in influencing the diabetes through food intake. (5)

Tunbridge states that the reasons why patients fail to maintain satisfactory control fall into three main categories psychological social and educational and that the psychological causes are especially prominent in the juvenile diabetic. He reiterates the belief that the trauma caused by the discovery of diabetes is deeper and more disturbing than the anxiety caused by other chronic diseases. (144)

Palmer emphasized the uniqueness of diabetes mellitus among chronic and incurable diseases. He stated that the diabetic is faced with interminable diet restriction which virtually eliminates many highly gratifying foods. There is no other disease which requires daily self administration of medication with a hypodermic syringe with the threat of disaster if this ritual is not observed. The nearness of disaster is further emphasized by the institution of daily urine testing in which the patient is confronted with evidence of any defection from strict control. The success and failure of diabetic control is largely dependent upon the active participation of the patient in the treatment. Obviously far more responsibility for the control of his disease is placed on the patient than in many other diseases (105)

Psychotherapy in diabetes

Authorities agree that more adequate treatment of diabetics requires an understanding of the patient as a person and not merely as a case of disturbed sugar metabolism

Bauch in the nineteen-thirties, appears to have been the first to attempt to develop systematic

psychotherapy for diabetics as a supplement to general medical care. He pointed out that sugar excretion is frequently the reaction of the patient to external and internal stimuli particularly those of an emotional nature, and that tension and irritability are common in the diabetic. He reports the systematic use of relaxation therapy (3) Jacobson calls attention to the fact that diabetic patients often display an extraordinary degree of restlessness and anxiety and states that relaxation therapy is indicated (71)

Herskowitz pointed out the importance of re education and encouragement and maintained that classes instituted for instruction in matters of diet and regimen are among the greatest aids in helping the mental hygiene of the diabetic patient (58) The refractory patient who disregards rules often calls for careful psychiatric study as the usual disciplinary approach may tend to aggravate the situation unless social and personality factors have been carefully evaluated (24)

In the nineteen-fifties Stearns stated that in most instances lack of success in diabetic control can be ascribed to inadequate co-operation of the patients, who do not follow the prescribed regimen satisfactorily. The precipitating factor however may be some action or attitude of the physician based on his lack of awareness of the real significance of the patient's behavior or lack of skill in handling the issues arising in the course of treatment. The author indicated that the diagnosis of diabetes means different things to different patients and that only a few approach the problem realistically. He suggested that it would be more effective to limit initial reassurance to emphasizing the positive aspects of the situation and to answering the questions asked by the patient in the least disturbing manner. The specific anxieties could be dealt with subsequently. The problem areas center around the necessity to follow a restricted diet and the necessity of insulin injections. (128)

Beaser reported that insulin therapy of diabetes may be complicated by emotional tensions. These may engender a variety of symptoms which tend to complicate the ambulatory treatment (5)

Dobson with his co-workers described a clinic set up for the better handling of the social economic and medical factors so important in the care of diabetic patients. This included the services of a social worker (33)

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Beaser points out that the diabetic's basic difficulty adhering to his diet is psychological rather than physiological. Also he adds even superficial psychiatric observation of diabetic patients reveals that many kinds of environmental and intra-psychic factors are important in influencing the diabetes through food intake. (5)

Tunbridge states that the reasons why patients fail to maintain satisfactory control fall into three main categories: psychological, social and educational and that the psychological causes are especially prominent in the juvenile diabetic. He reiterates the belief that the trauma caused by the discovery of diabetes is deeper and more disturbing than the anxiety caused by other chronic diseases. (144)

Palmer emphasized the uniqueness of diabetes mellitus among chronic and incurable diseases. He stated that the diabetic is faced with interminable diet restriction which virtually eliminates many highly gratifying foods. There is no other disease which requires daily self-administration of medication with a hypodermic syringe with the threat of disaster "if this ritual is not observed. The nearness of disaster is further emphasized by the institution of daily urine testing, in which the patient is confronted with evidence of any defection from strict control. The success and failure of diabetic control is largely dependent upon the active participation of the patient in the treatment. Obviously far more responsibility for the control of his disease is placed on the patient than in many other diseases. (105)

Psychotherapy in diabetes

Authorities agree that more adequate treatment of diabetics requires an understanding of the patient as a person and not merely as a case of disturbed sugar metabolism.

Bauch, in the nineteen-thirties appears to have been the first to attempt to develop systematic

psychotherapy for diabetes as a supplement to general medical care. He pointed out that sugar excretion is frequently the reaction of the patient to external and internal stimuli particularly those of an emotional nature, and that tension and irritability are common in the diabetic. He reports the systematic use of relaxation therapy. (3) Jacobson calls attention to the fact that diabetic patients often display an extraordinary degree of restlessness and anxiety and states that relaxation therapy is indicated. (71)

Herskowitz pointed out the importance of re-education and encouragement, and maintained that classes instituted for instruction in matters of diet and regimen are among the greatest aids in helping the mental hygiene of the diabetic patient. (58) The refractory patient who disregards rules often calls for careful psychiatric study as the usual disciplinary approach may tend to aggravate the situation unless social and personality factors have been carefully evaluated. (24)

In the nineteen-fifties Stearns stated that in most instances lack of success in diabetic control can be ascribed to inadequate co-operation of the patients who do not follow the prescribed regimen satisfactorily. The precipitating factor however may be some action or attitude of the physician based on his lack of awareness of the real significance of the patient's behavior or lack of skill in handling the issues arising in the course of treatment. The author indicated that the diagnosis of diabetes means different things to different patients, and that only a few approach the problem realistically. He suggested that it would be more effective to limit initial reassurance to emphasizing the positive aspects of the situation and to answering the questions asked by the patient in the least disturbing manner. The specific anxieties could be dealt with subsequently. The problem areas center around the necessity to follow a restricted diet and the necessity of insulin injections. (128)

Beaser reported that insulin therapy of diabetes may be complicated by emotional tensions. These may engender a variety of symptoms which tend to complicate the ambulatory treatment. (5)

Dobson with his co-workers described a clinic set up for the better handling of the social, economic and medical factors so important in the care of diabetic patients. This included the services of a social worker. (33)

Psychosomatic research on diabetes mellitus in children

According to Kesler more, perhaps, has been written about diabetes from the psychological standpoint than about any other childhood disease, excluding those considered psychosomatic. The major concerns have been: 1) the relationship between the emotions and the medical course of the diabetes and 2) emotional reactions to the management of the illness. (80)

Dietary restrictions and the daily injections of insulin are liable to cause many problems. The mother's relationship with her child is strained by prohibitions of certain foods and infliction of pain at the injection. Children are apt to attribute the illness to eating too many sweets and so may feel guilty. Similarly if the sugar metabolism gets out of control, both the parents and the child may feel guilty.

In two of the cases studied by Daniels, diabetes occurred in childhood at a time when an *anxiety neurosis* appeared to be acute. The factor precipitating the neurosis may also conceivably have precipitated the diabetes. Thus there actually was a link between the neurosis and the onset of diabetes certainly could not be proved. (24)

Fischer and Dolger described dullness, immaturity and dependency as characteristics of young diabetic patients. (44) Benedek suggested that no chronic disease of childhood produces more anxiety in the mother than diabetes mellitus. (9) On the other hand in Konach's view virtually all parents of physically handicapped children have a feeling of guilt and of personal responsibility for the handicap. (82)

Bruch stated that the need for adequate metabolic treatment of the diabetic condition so as to insure more normal growth and freedom from physical ill-health had long stood in the foreground of medical thinking, but it was only in the nineteen-forties that the psychological problems of diabetic children had gained attention. Her own observations were made on 37 diabetic children. As was the fashion in psychosomatic medicine at that time, she was concerned with a specific personality structure in diabetic children and psychological characteristics of the family setting in which diabetes had developed. One focus of Bruch's inquiry was upon factors which may have been of traumatic significance in the development of diabetes. There were disturbances in family relationships, such as divorce, birth of

a sibling, death, boarding out with relatives etc., in 10 of the 37 cases. Only in one case had the family connected this event with the onset of diabetes, while in another case a relationship was later suspected between the onset of diabetes and the child's separation from the father who had played an affectionate role in the life of his son.

As Bruch remarked, if the disease had existed for several years it is difficult, if not impossible, to differentiate between the pre-existing psychological picture and the influence of the diabetic regimen on the family. She differentiated three main ways in which the mothers reacted towards the diabetic regimen.

1 *A tolerant and relaxed acceptance of the responsibility* This attitude seemed to produce fairly satisfactory regulation and adjustment in the children. While it may be recognized as the most desirable attitude, it was the least frequent in Bruch's cases.

2 *A perfectionistic overcontrol* With this attitude, all tasks become expressions of the mother's absolute need to do the right thing. Here the basic attitude toward the child is aggressive and subduing. Yet this overcontrol of the child was characteristically associated with satisfactory regulation of the diabetes, and these families were rated as good and co-operative. Frequently behavior difficulties occurred in other fields, such as stealing, poor school-work or sudden rebelliousness.

3 *Erratic or persistently poor co-operation regarding the medical regimen*. Such an attitude of course produced poor control, with marked fluctuation in the degree of regulation. Satisfactory regulation was always the exception. Despite these consequences, this attitude was the most frequent. (18)

Since the nineteen-forties, many authors have stressed the psychological problems of young diabetics.

Mason called attention to the existence of diabetes as the background illness for suicidal behavior in three disturbed adolescent girls. (92)

Katz mentioned the greater incidence of behavior problems in diabetic than in nondiabetic children. (77)

Stearns pointed out that many young diabetics exhibit a gamut of unreasonable behavior which can be interpreted as essentially self-destructive. Such behavior was most frequently exhibited when major life adjustments had to be made

and was more likely to occur when the emotional and socio-economic environment was suboptimal. (129)

Etravler and Sines in their survey of juvenile diabetes reported rebellious and resentful behavior in 12 per cent of their cases (39)

Sterky undertook a study to find out whether diabetic children have an increased frequency of emotional disturbances and, if so what factors in the diabetic state might have influenced the symptoms. His group of diabetic children had a significantly increased frequency of psychologically disturbed mothers who chiefly displayed various anxiety symptoms. The frequency of children without reported psychological symptoms was the same in the diabetic as in the nondiabetic control group. School achievements were found to be equal in the two groups and were not influenced by the age at the onset of diabetes. Cases with "poor" diabetic control were found to have psychological symptoms more often than those with fair control. (132)

Knowles and his co-workers reported that thirteen of ninety two juvenile diabetics exhibited an excessive drive for self assertion. They rebelled against authority overate were self-destructive and went to great lengths to attract attention. It seemed as if diabetes aggravated the usual teen-age drive for recognition. Hostility was first directed towards parents and later towards teachers and employers. Job-holding was frequently difficult. Another group of thirteen patients suffered from severe hidden anxiety. They had great difficulty in accepting the fact that they had diabetes and, consequently denied the disease. (81)

Hinkle and co-workers in a panel discussion stated that the impact of diabetes mellitus on the younger child is at first purely physical because getting an injection hurts. As the child becomes older the so-called "stigma" of being a diabetic becomes increasingly significant and attempts are made to keep the condition secret. The panel members thought that girls were more likely to be secretive in this respect. (65)

Fischer pinpoints the factors which were found to be most important as causes of emotional disturbance in a group of diabetic children. These were 1) dietary restrictions 2) the need for insulin injections 3) urinalysis, 4) the limitations of the daily activities that diet and

insulin impose 5) the stigma of being a diabetic, 6) the future outlook for a diabetic child (development of complications: cardiovascular, neurologic, renal). In his opinion diabetic children do not seem to do as well in school and do not achieve success in college or professional training although it cannot be said definitely whether this is due to physical or psychological factors. There are, of course, exceptions to this general pattern of achievement. (45)

Greenberg and Blair pointed out the numerous difficulties in the treatment of childhood diabetes. The emotional difficulties seem to arise from the presence of the diabetes and the effect this has on family relationships as well as on the child himself. (53)

Falstein and Judas reported the treatment of two juvenile diabetics and demonstrated the development of a highly pathologic mother-child relationship resulting from the diabetic management. They emphasized the need for a multidisciplinary approach to the problems of diabetes. (42)

Davis and co-workers attempted to evaluate the attitude of children with diabetes mellitus and its treatment. Their findings suggest that diabetic boys and girls may consider their disorder a normal part of their lives without really comprehending its seriousness. The fact that the impact of having a serious long-term illness either was not fully recognized or was "successfully" denied, by this group of children was demonstrated by their preference for diabetes over several far less serious conditions, e.g., constipation, acne or obesity. (30)

Psychological research on childhood diabetes mellitus

Brown in 1938 in his group of diabetic children found no significant deviation in intelligence from that of their sibling controls or from the average of Minneapolis children (as determined by Stanford-Binet test). (15)

More recently studies of the childhood diabetic personality by Kubany and co-workers (83) and of their mental health by Sterky (132) revealed no average changes from normal. On the other hand Swift and Seidman employing both psychologic and psychiatric methods presented evidence of deviation from the normal. (134) Ack and Weil found a significant negative difference in the Stanford-Binet intelligence

scale scores of diabetics as compared with their siblings, but only in children who had acquired the disease before the age of five years. The authors suggest two possible explanations.

1. *Physiologically* the brain tissues of the young diabetic patient may be impaired by metabolic disturbances which do not produce brain damage in older diabetic children.

2. *Psychologically* the impact of the realization of chronic disease on the young child's immature ego may result in some loss of IQ (1)

Weil and Ack reported on school achievement in cases of juvenile diabetes mellitus. They

compared diabetic children with their non-diseased siblings in regard to their scholastic achievement and related the results to their previously determined intelligence quotients. They found that the diabetic children as well as their siblings had achievement scores which were not significantly different from what might be expected with their intelligence quotients. There was no difference from their siblings in the achievement levels of the diabetic children, either as a single group or when classified on the basis of age at onset or duration of the disease. They concluded that the etiology of the school problems was not related to scholastic achievement. (146)

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During the gathering of the series it soon became evident that the number of diabetically well controlled cases in the clinic population exceeded the number of poorly controlled cases. Because of this, all poorly controlled cases which were hospitalized during the study were included in the material. There were 28 such cases. 2 cases (Nos. 16 and 53) were added to the material from the out-patient clientele because in these cases, Mauriac syndrome was a sign of poor diabetic control. There were altogether 3 cases in the P group diagnosed as Mauriac's syndrome.

Marfan's syndrome, consisting of dwarfism, hepatomegaly and obesity is a throat exception connected with poor diabetic control (41).

Of the diabetically well controlled children, 27 were hospitalized during the time of the study either for diabetes or for some other illness, and the remaining 3 (Nos. 3, 50 and 56) were added to the material from the out-patient clientele, being selected to match for age and sex as closely as possible the P group.

METHODS

1 Interviewing the parents

If the child was hospitalized, the interviews with the parent(s) were usually arranged through the hospital personnel at convenient time, usually before or after the regular visiting hours. If the child was visiting the out-patient clinic, the author sent a letter in advance to the parent usually the mother asking for her co-operation in the study. If the parent did not answer the first call he usually responded to the second. Finally, not a single case had to be excluded because of poor co-operation.

The mothers (in 47 cases) the fathers (in 4 cases) or both parents (in 9 cases) were interviewed by the author. Of the 39 possible cases (the mother of one of the poorly controlled children was deceased) the mothers of 3 children could not be reached. These were all cases in which the father alone was responsible for bringing the child to the hospital or to the out-patient clinic. The reason for the mother's absence was

- in two cases the care of younger siblings and
- in one case the mother's working hours away from home

The number of interviews ranged from one to twelve. In those cases where the parent(s) was seen only once, a special questionnaire was gone through. This questionnaire is presented as one of the Appendices to this thesis. In those cases in which the parent(s) was seen more than once, the same questionnaire was gone through usually during the last interview in order to get comparable data from the interviews.

2 Interviewing the child

If the child was hospitalized, the time for the interview was arranged so as not to disturb other ward activities. If the child visited the out-patient clinic the author sent a letter in advance to the parents or to the child, asking for an interview.

Every child had at least one psychiatric interview or play observation by the author. The interview technique with the children was relatively non-directive. If the child suffered from marked separation anxiety the parents were allowed to be present in the interviewing room for a few minutes. The younger children were introduced to von Staubs anatomical or drawing equipment. The older children could choose between drawing and talk. In those cases where the child chose either play or drawing, this was followed by a period of discussion. During this discussion the reason for the child's coming to the interview, his feelings and thoughts about his diabetes, and his eating habits were touched upon.

Table 2 A. shows the number of interviews with parents in the GF and P groups respectively. Table 2 A. Number of interviews with parents.

	GF	P	Total
1 interview with the mother	9	9	18
2 or 3 interview with the mother	13	11	24
4 or more interviews with the mother	3	3	6
1 interview with the father	—	2	2
2 or 3 interviews with the father	1	1	2
1 interview with the mother + 1 interview with the father	1	2	3
2 interviews with both parents	1	—	1
3 interviews with the mother + 1 interview with the father	—	1	1
4 or more interviews with the mother + 1 interview with the father	1	1	2
3 interviews with both parents	1	—	1

Material and methods

MATERIAL

The series collected consisted of 60 diabetic children all attending the diabetic outpatient clinic of the Children's Hospital University of Turku. The patients visiting this University Hospital come mainly from Turku and the surrounding small towns and country communities. The total outpatient diabetic population as to December 31, 1967 was 176 patients. Thus this series represents roughly one-third of the total number.

Gathering of the series took place between September 1964 and December 1967. The cases were selected on the basis of the following criteria:

1 *Age* Children under 3 years of age at the time of the psychological examination were excluded because of the difficulty of giving and analyzing the psychological tests.

2 *Duration of the disease* Since the purpose of the study was to examine the parent's coping

processes and the children's later adjustment it was decided to confine the series to children who at the time of the last examination, had been diagnosed as diabetic for at least one year.

3 *The diabetic control* All cases over five years of age in whom diabetes had been diagnosed at least one year previously were classified into two groups in terms of diabetic control:

- a. Good or Fair Control (abbreviated as GF)
- b. Poor Control (abbreviated as P)

The criteria for diabetic control closely resemble those of Gamstorp and co-workers (48) and are presented in Table 1. To be considered GF the patients had to meet four of the five criteria listed below. In Table 1. Correspondingly, to be considered P the patients had to meet four of the five criteria listed in Table 1.

Table 1. The criteria for adequacy of diabetic control.

	GF	P
Growth	Normal or greater than the tenth percentile for age	Below the tenth percentile for age
Acetonuria	Urine free of acetone 50 to 75 per cent of the samples collected	Acetonuria more than 50 per cent of the samples collected
24-hour urine glucose	Less than 30 g	Greater than 30 g
Fasting blood sugar level	Up to 200 mg per 100 ml	More than 200 mg per 100 ml
Number of hospitalizations per year for control of diabetes	No more than one hospitalization per year	More than one hospitalization per year

Growth The height at the time of the last examination was compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74).

Acetonuria The urine was tested for acetone each time the child visited the outpatient clinic. In addition to this the urinalysis for acetone

(a tape test) was performed at home every morning or every other morning and the results written down in a notebook which the child then brought with him to the clinic.

24-hour quantitative urine glucose This was measured each time the child visited the outpatient clinic.

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3 interviews with both parents	1	—	1
	20	30	60

Table 2 B shows the number of interviews with the children in the GF and P groups respectively

Table 2 II Number of interviews with the children

	GF	P	Total
1 interview with the child	12	10	22
2 or 3 interviews with the child	13	17	30
4 or more interviews	5	3	8
	30	30	60

The average number of interviews per family was 4.2

3 Supplementary information

The information obtained in the interviews was supplemented by the hospital records and records from the outpatient clinic 6 children had received treatment at other hospitals. In these cases the records of these hospitals were placed at the authors disposal.

During the childrens hospital stays the author had weekly conferences with the occupational therapist who observed the children in group situations

4 Psychological tests

Three psychological tests were administered to all the children an intelligence test (Terman-Merrill Lehtovaara) and two projective techniques — the Rosenzweig Picture Frustration Test and the Holzman Inkblot Technique Two psychologists performed the psychological testing of the children. One of them conducted all the Holzman Inkblot Tests all the Rosenzweig Picture Frustration tests and 33 of the intelligence tests

The other psychologist conducted the intelligence tests in 26 cases One of the parents had undergone a psychological test with a third psychologist at the time of the investigation. Because the test result was available to the author it was felt unnecessary to repeat that child's intelligence test The external conditions in which the testing was carried out were standardized as possible in the same room at the hospital. There were four exceptions to this two children were tested at their schools one at his home and the fourth in the communitys public health clinic All were children who visited the outpatient clinic very infrequently

and reaching them out in their own home communities considerably shortened the time of the investigation.

The examinations were conducted in two sessions each lasting approximately one hour The psychologists did not know at the time of the examination, which diabetic group the child belonged to

5 Teachers assessment

With the permission of the parent, a questionnaire was sent to the child's teacher in every case in which the child attended school. This questionnaire is presented in the "Appendixes of this paper The teacher was asked to evaluate the child's school achievement and some aspects of the child's behavior at school. Teacher participation was exceptionally good. All teachers responded in a matter of several days or a few weeks either returning the completed questionnaire or contacting the author by phone.

6 Statistical methods

The statistical methods employed on the medical social and sociopsychiatric data were limited to statistical hypothesis testing The data of these parts of the research were in most cases classificatory or measured in an ordinal scale. This fact led to the use of nonparametric methods (in this case the chi test) Parametric tests were chosen only in two cases (t test for data in Tables 3 and 4)

The test used in calculating the Rosenzweig Picture Frustration results was the t test.

For the analysis of the Holzman Inkblot Technique scores the method of Discrimination Analysis was used In this method the position of every subject is estimated in relation to the line that best separates the two groups Mahalanobis D^2 and associated F statistics were computed to test the group differences Because the scores are frequency counts of responses they were assumed to approach the Poisson distribution. The Freeman-Tukey square root transformation was used as suggested by Mosteller and Bush (100) That is $z = \sqrt{X} + \sqrt{X+1}$ where X is the observed frequency score

The analysis was computed at the Northern Europe University Computing Center Lyngby Denmark, (Proj No 403026) using the BDM 04M computer program

CHARACTERISTICS OF THE SERIES

Age distribution. Figure 1 shows the age distribution of the patients at the time of the last examination.

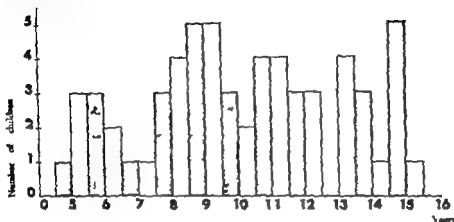


Fig. 1 Age distribution at the time of the last examination (years) in the GF group (white bars) and in the P group (shaded bars)

Average age at the time of the last examination was 11 yrs 4 mos in the GF group and 10 yrs 8 mos in the P group.

Sex distribution. There were 14 boys and 16 girls in the GF group and 15 boys and 15 girls in the P group.

Place of residence. Table 2 shows the place of residence of the patients in the GF group and the P group respectively.

Table 2. Place of residence.

Place of residence	GF	P	Total
Turku	6	6	12
Country town	6	7	13
Country community	18	17	35
	30	30	60



Figure 2 shows the map of the area in South-West Finland served by our Children's Hospital.

Figure 2. Map of South-West Finland

Table 2 B shows the number of interviews with the children in the GF and P groups respectively

Table 2 B Number of interviews with the children

	GF	P	Total
1 Interview with the child	12	10	22
2 or 3 interviews with the child	13	17	30
4 or more interviews	5	3	8
	30	30	60

The average number of interviews per family was 4.2

3 Supplementary information

The information obtained in the interviews was supplemented by the hospital records and records from the outpatient clinic. 6 children had received treatment at other hospitals. In these cases the records of these hospitals were placed at the author's disposal.

During the children's hospital stays the author had weekly conferences with the occupational therapist who observed the children in group situations.

4 Psychological tests

Three psychological tests were administered to all the children: an intelligence test (Terman-Merrill Lehtovaara) and two projective techniques — the Rosenzweig Picture Frustration Test and the Holzman Inkblot Technique. Two psychologists performed the psychological testing of the children. One of them conducted all the Holzman Inkblot Tests, all the Rosenzweig Picture Frustration tests and 33 of the intelligence tests. The other psychologist conducted the intelligence tests in 26 cases. One of the patients had undergone a psychological test with a third psychologist at the time of the investigation. Because the test result was available to the author it was felt unnecessary to repeat that child's intelligence test. The external conditions in which the testing was carried out were standardized as possible in the same room at the hospital. There were four exceptions to this: two children were tested at their schools, one at his home and the fourth in the community's public health clinic. All were children who visited the outpatient clinic very infrequently

and reaching them out in their own home communities considerably shortened the time of the investigation.

The examinations were conducted in two sessions each lasting approximately one hour. The psychologists did not know at the time of the examination, which diabetic group the child belonged to.

5 Teachers' assessment

With the permission of the parent a questionnaire was sent to the child's teacher. In every case in which the child attended school. This questionnaire is presented in the Appendixes of this paper. The teacher was asked to evaluate the child's school achievement and some aspects of the child's behavior at school. Teacher participation was exceptionally good. All teachers responded in a matter of several days or a few weeks, either returning the completed questionnaire or contacting the author by phone.

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The statistical methods employed on the medical, social and sociopsychiatric data were limited to statistical hypothesis testing. The data of these parts of the research were in most cases classificatory or measured in an ordinal scale. This fact led to the use of nonparametric methods (in this case the chi-test). Parametric tests were chosen only in two cases (t-test for data in Tables 3 and 4).

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The analysis was computed at the Northern Europe University Computing Center, Lyngby, Denmark (Proj. No. 403026) using the BDM 04M computer program.

Duration of illness

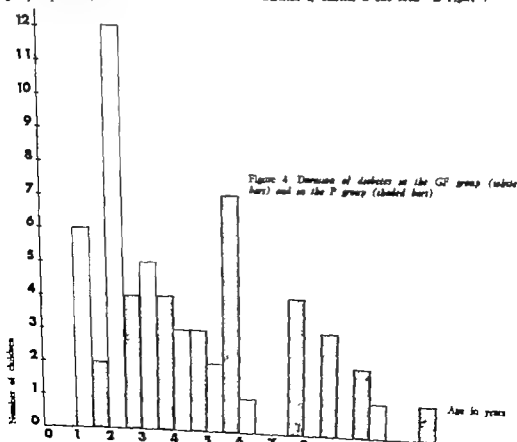
Table 4 shows the duration of diabetes in the cases of the series.

Table 4 Duration of illness.

Duration of diabetes			GF	P	Total
1 yr to 1 yr 11 mo			6	2	8
2 yrs to 2 yrs 11 mo			12	4	16
3 yrs to 3 yrs 11 mo			5	4	9
4 yrs to 4 yrs 11 mo			3	3	6
5 yrs to 5 yrs 11 mo			2	7	9
6 yrs to 6 yrs 11 mo			1	—	1
7 yrs to 7 yrs 11 mo			—	4	4
8 yrs to 8 yrs 11 mo			—	3	3
9 yrs to 9 yrs 11 mo			—	2	2
10 yrs to 10 yrs 11 mo			1	—	1
11 yrs to 11 yrs 11 mo			—	1	1
			30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo. There is a significant difference between the groups ($p < 0.05$).

Duration of diabetes is also shown in Figure 4.



Results

1 Medical data

Table 3 shows the age at the diagnosis of diabetes
Table 3 Age at the diagnosis of diabetes.

Age at diagnosis	GF	P	Total
2 yrs to 2 yrs 11 mo	—	7	7
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	1	6	7
5 yrs to 5 yrs 11 mo	1	1	2
6 yrs to 6 yrs 11 mo	3	4	7
7 yrs to 7 yrs 11 mo	6	4	10
8 yrs to 8 yrs 11 mo	3	—	3
9 yrs to 9 yrs 11 mo	3	1	4
10 yrs to 10 yrs 11 mo	1	2	3
11 yrs to 11 yrs 11 mo	4	—	4
12 yrs to 12 yrs 11 mo	2	—	2
13 yrs to 13 yrs 11 mo	—	1	1
14 yrs to 14 yrs 11 mo	1	—	1
	30	30	60

Average age at the diagnosis in the G F group was 8 yrs 1 mo and in the P group 5 yrs 5 mo. There is a statistically significant difference between the groups ($p < 0.02$).

This is in accordance with the general observation that diabetes is more difficult to control in the young child than in the older child.

In the cases of this series all the children who had developed diabetes prior to the age of three years have poor control of their illness.

Age at diagnosis also shown Figure 3

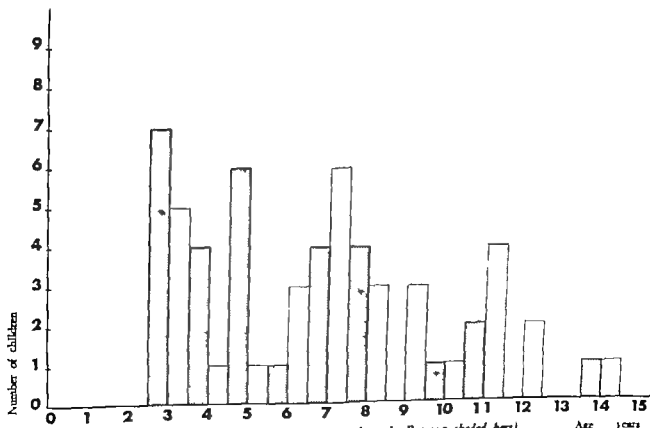


Figure 3 Age at diagnosis in the GF group (white bars) and in the P group shaded bars

Duration of illness

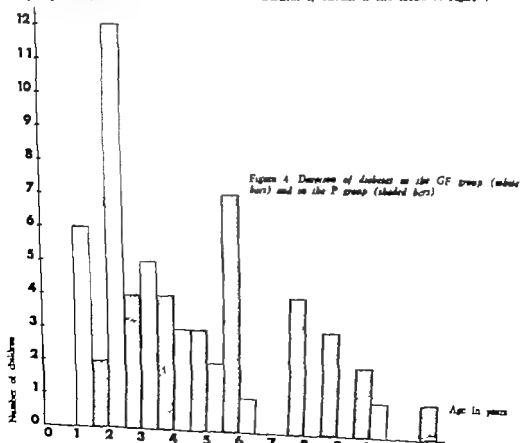
Table 4 shows the duration of diabetes in the cases of the series.

Table 4 Duration of illness.

Duration of diabetes						GF	P	Total
1 yr	to	1 y	11 mo			6	2	8
2 yrs	to	2 yrs	11 mo			12	4	16
3 yrs	to	3 yrs	11 mo			5	4	9
4 yrs	to	4 yrs	11 mo			3	3	6
5 yrs	to	5 yrs	11 mo			2	7	9
6 yrs	to	6 yrs	11 mo			1	—	1
7 yrs	to	7 yrs	11 mo			—	4	4
8 yrs	to	8 yrs	11 mo			—	3	3
9 yrs	to	9 yrs	11 mo			—	2	2
10 yrs	to	10 yrs	11 mo			1	—	1
11 yrs	to	11 yrs	11 mo			—	1	1
						30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo. There is significant difference between the groups ($p < 0.05$).

Duration of diabetes is also shown in Figure 4



Results

1 Medical data

Table 3 shows the age at the diagnosis of diabetes

Table 3 Age at the diagnosis of diabetes

Age at diagnosis					GF	P	Total
2 yrs	to	2 yrs	11 mo		—	7	7
3 yrs	to	3 yrs	11 mo		5	4	9
4 yrs	to	4 yrs	11 mo		1	6	7
5 yrs	to	5 yrs	11 mo		1	1	2
6 yrs	to	6 yrs	11 mo		3	4	7
7 yrs	to	7 yrs	11 mo		6	4	10
8 yrs	to	8 yrs	11 mo		3	—	3
9 yrs	to	9 yrs	11 mo		3	1	4
10 yrs	to	10 yrs	11 mo		1	2	3
11 yrs	to	11 yrs	11 mo		4	—	4
12 yrs	to	12 yrs	11 mo		2	—	2
13 yrs	to	13 yrs	11 mo		—	1	1
14 yrs	to	14 yrs	11 mo		1	—	1
					30	30	60

Average age at the diagnosis in the GF group was 8 yrs 1 mo and in the P group 5 yrs 5 mo. There is a statistically significant difference between the groups ($p < 0.02$)

This is in accordance with the general observation that diabetes is more difficult to control in the young child than in the older child.

In the cases of this series all the children who had developed diabetes prior to the age of three years have poor control of their illness.

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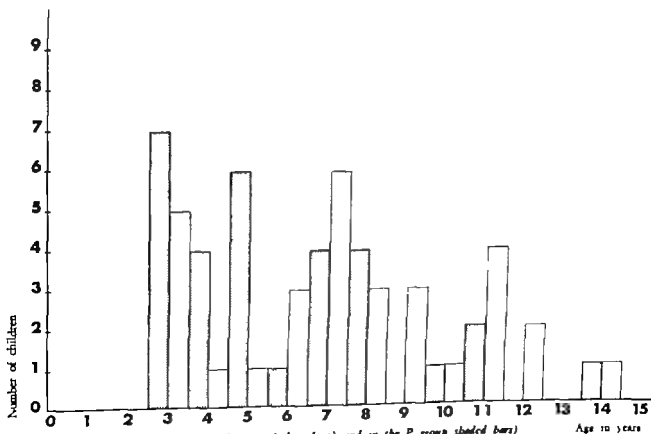


Figure 3 Age at diagnosis in the GF group (white bars) and in the P group (shaded bars)

Age in years

Duration of illness

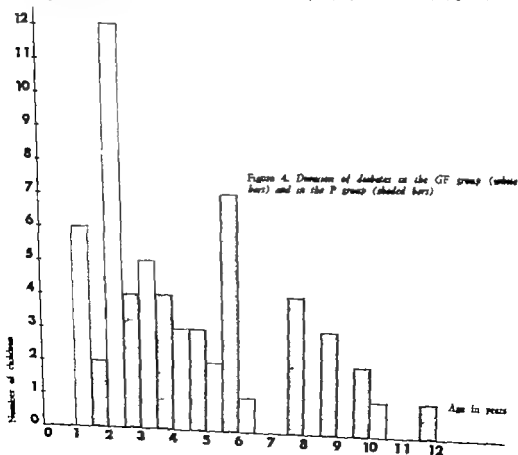
Table 4 shows the duration of diabetes in the cases of the series.

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Duration of diabetes			GF	P	Total
1	yr	to 1 yr 11 mo	6	2	8
2	yr	to 2 yrs 11 mo	12	4	16
3	yr	to 3 yrs 11 mo	5	4	9
4	yr	to 4 yrs 11 mo	3	3	6
5	yr	to 5 yrs 11 mo	2	7	9
6	yr	to 6 yrs 11 mo	1	—	1
7	yr	to 7 yrs 11 mo	—	4	4
8	yr	to 8 yrs 11 mo	—	3	3
9	yr	to 9 yrs 11 mo	—	2	2
10	yr	to 10 yrs 11 mo	1	—	1
11	yr	to 11 yrs 11 mo	—	1	1
			30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo. There is significant difference between the groups ($p < 0.05$).

Duration of diabetes is also shown in Figure 4.



Heredity

Table 5 shows the occurrence of known cases of diabetes among the relatives of the children of the two groups

Table 5 Relatives with diabetes

	GF	P	Total
Diabetes in first degree relatives	8	14	22
Diabetes in more distant relatives	8	7	15
No known diabetic relatives	14	9	23
	30	30	60

The term first degree relatives in this study includes the patient's siblings parents grand parents and first cousins. There is no statistically significant difference between the groups.

The series included six families in which more than one child is affected with diabetes. Table 6 shows these cases distributed according to diabetic control.

Table 6 Diabetic control in siblings

Number of families	GF	P	Ungrouped	Total
6	3	7	3	13

These six families as is shown in Table 6 have altogether 13 diabetic children. Of these 13 children 9 are included in the material.

Four are excluded for the following reasons: In two cases the diabetes was of less than one year's duration in another case the child was so young that it was not possible to give her psychological tests used in this study and in the remaining case the patient was over fifteen years old at the time of the study.

Growth

In the present investigation the data on height at the time of diagnosis of diabetes and at the time of the last examination have been obtained. These figures have been compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74). Table 7 shows the comparative heights at the time of diagnosis for the GF and the P groups respectively.

Table 7 Height at the diagnosis of diabetes.

	GF	P	Total
Height above normal	3	—	3
normal	26	30	56
below normal	1	—	1
	30	30	60

Table 8 shows the heights of the two groups at the time of the last investigation.

Table 8 Height at the time of the last investigation

	GF	P	Total
Height above normal	—	—	—
normal	29	23	52
below normal	1	7	8
	30	30	60

The frequency of stunted growth at the time of the last examination in the series is 13.3 % (3.3 % in the GF group and 23.3 % in the P group).

The figures presented in Tables 7 and 8 are too small for statistical treatment. Moreover they cannot be considered as final figures because the majority of the patients have not yet reached adult stature. There is however a tendency for the heights to be below the lower normal limit in the P group. In the GF group there is only one child whose height at the time of the last investigation was below normal. This is the same child whose height was already below the lower normal limit at the diagnosis of diabetes (Table 7). The growth retardation observed in the P group may thus in some way be connected with the control of the diabetes.

2 Social and socio psychiatric data Size of the family

Table 9 shows the total number of children in the families of the GF and the P groups respectively.

Table 9 Total number of children.

Number of children	GF	P	Total
1 child	2	5	7
2 children	8	4	12
3 children	9	7	16
4 to 5 children	4	6	10
6 to 8 children	5	8	14
9 to 11 children	1	—	1
	30	30	60

Birth rank

Table 10 shows the birth rank of diabetic children in the GF and the P groups respectively.

Table 10 Birth rank.

	GF	P	Total
Only child	2	5	7
Youngest child	8	9	17
Eldest child	11	3	14
Middle child	9	13	22
	30	30	60

According to these findings it is relatively rare for an eldest child's diabetes to be poorly controlled. Of the 14 diabetic eldest children in the series 11 were well or fairly controlled, whereas only 3 were poorly controlled. The difference is statistically almost significant ($p < 0.10$) (In the statistical calculation the only child category has been omitted.) The reason for this can not be stated categorically but we may speculate that it is psychological. The reason may be suggested to be the responsibility placed upon the eldest child in the family an attitude which he carries over to the care of his disease. Two of the three poorly controlled eldest children developed diabetes during the mother's second pregnancy or a few weeks after the birth of the second child into the family. It can be supposed that in these cases the characteristic attitudes of the eldest child in the family had not developed prior to the onset of the disease.

Social status of the family

In this study the social categories established by the Statistical Bureau for the City of Helsinki and for Espoo are used. They are based on the social esteem felt to be achieved by different vocations. According to these categories Persons in professional and managerial positions belong

to Group I. Persons directing small enterprises, foremen, higher office personnel, etc., belong to Group II. Skilled workmen lower office personnel, etc., belong to Group III and unskilled workmen to Group IV (56).

Table 11 shows the social grouping of the families in the GF and the P groups respectively.

Table 11 Social groups.

	I	II	III	IV	Total
GF	1	4	20	5	30
P	2	10	16	2	30
	3	14	36	7	60

When in the statistical calculations Social Groups I and II were combined, and, similarly Social Groups III and IV it was discovered that the two upper social groups were more frequently found in the P category than in the GF category. Accordingly the two lower social groups were more frequent in the GF category than in the P category. The difference is statistically significant ($p < 0.05$).

In the following table the social grouping of the study material is compared with the social grouping of Helsinki City and Espoo, 1965. There are the only comparable data available, because only two communities in Finland, Helsinki and Espoo, have statistics on the social grouping of their inhabitants.

Table 12. Social grouping compared with the social grouping of Helsinki and Espoo

	I	II	III	IV	Unknown
Social groups in the study material	5 %	23.3 %	60 %	11.7 %	
Social groups in Helsinki	18.8 %	23.1 %	40.4 %	13.4 %	4.3 %
Social groups in Espoo	21.5 %	22.2 %	37.8 %	12.3 %	6.2 %

As can be seen from the above figures the greatest differences from the comparison populations are found in Social Groups I and III. It can be supposed, however that in Helsinki and Espoo the incidence of professional and mana-

gerial positions is higher than in small communities. Further in the series the number of children of small farmers, belonging to group III, is rather high.

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Four are excluded for the following reasons: in two cases the diabetes was of less than one year's duration; in another case the child was so young that it was not possible to give her psychological tests used in this study; and in the remaining case the patient was over fifteen years old at the time of the study.

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3 children	9	7	16
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6 to 8 children	6	8	14
9 to 11 children	1	—	1
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	GF	P	Total
Only child	2	5	7
Youngest child	8	9	17
Eldest child	11	3	14
Middle child	9	13	22
	30	30	60

The children's emotional health before the onset of diabetes

Table 15 shows the incidence of neurotic and characterological symptoms in the children before the onset of diabetes.

Table 15 Neurotic and characterological symptoms in the children before the onset of diabetes.

	GF	P	Total
Enuresis	—	4	4
Encopresis	—	1	1
Enuresis and encopresis	1	—	1
Anxiety state, childhood phobias	—	1	1
Behavioral disturbances (delinque, hitting out at once)	1	—	1
	2	6	8

There are considerable differences of opinion in the literature regarding the age at which a child should be labeled enuretic or encopretic. In this study the data obtained by Roffman in a Swedish population are used: the age limits for enuresis (<4 years) and for encopresis between 3 and 4 years (8).

Although the figures in Table 15 are far too small for any conclusions it might be noted that in this series the children who later developed poor control of their diabetes had slightly higher incidence of enuresis at the time of onset of diabetes.

Moreover it is a common observation that some of the more permanent personality disorders are easily overlooked or wrongly interpreted as transient by the parents.

3 The family is in a state of confusion and is in a state of confusion.

There is a state of confusion.

By means of interviews with parents as well as by observing them during the visiting hours on the ward an attempt was made to learn how the parents reacted to the fact that their child had diabetes. For most of the parents the feeling was bewilderment and even shock, and many felt sad and depressed. In the following the most typical responses of the parents are presented with the inner feelings which, in the author's opinion, they reflected.

Bewilderment and shock. As if everything

This is especially true in the case of young children. Because of the significantly earlier age of onset in the P group a greater number of disturbed children belonging to that group may not have been included in the figures.

Emotional stress as a precipitating factor

Table 16 shows the known incidence of different stressful life situations in the cases of the series.

Table 16. Types of stressful life situations

	GF	P	Total
Death of a relative	2	1	3
Starting school	1	1	2
Birth of a sibling	3	1	4
Separation from home	—	1	1
Family move to another locality	—	1	1
Physical injury intrinsically harmless, but shocking for the child	—	1	1
Sibling seriously injured in traffic accident	—	1	1
	6	7	13

The cases marked) are those where the mother or the child spontaneously connected the event with the onset of the child's diabetes.

As is shown in Table 16 the incidence of stressful life situations prior to diagnosing the child's diabetes is about the same in both diabetic groups.

had stopped. As if blank wall had risen in front of me. "Everything was in confusion.

Anxiety and fears. "I myself will be taken to mental hospital." "I am afraid of the insulin injection. I fear the diet.

Depressive feelings. "We were gut down for a long time." "We thought he might die in the hospital."

Guilt feelings both realistic and unrealistic, were found in connection with depressive feelings. They were conveyed in the following statements.

Realistic guilt feelings. Mother was working long hours outside of the home and did not have time to take the child to the doctor earlier.

Unrealistic guilt feelings. "The child was breast fed for more than 1½ years, was it

Mother's employment

Of the 60 children included in the study the mothers of 46 worked solely at home. 25 of these 46 children belonged to the GF group and 21 to the P group. The mothers of another 5 children in the GF group and of 6 children in the P group held full time jobs away from home. In another 2 of the P group cases the mothers were working part time outside the home. In the last case the mother of the diabetically poorly controlled child is dead.

Table 13 shows the mother's employment for the GF and the P groups respectively

Table 13 Mother's employment

	GF	P	Total
Housewife	25	21	46
Part time away from home	—	2	2
Full time away from home	5	6	11
Mother deceased	—	1	1
	30	30	60

The overall incidence of mothers working away from home is 22 % (16 % in the GF group and 28 % in the P group). These figures are relatively low when compared with the overall incidence of married women in gainful employment in Finland. Exact comparative data can be obtained only from the Statistical Bureau of the city of Helsinki where in 1965 56 % of married women were working away from home.

This difference can be partly explained by the fact that our Children's Hospital serves a large number of country communities as well as the city of Turku itself. A high proportion of the population in these communities are farmers. 14 of the diabetics in the series are the children of small farmers and the mothers take an active part in the farm work.

There are of course many other factors affecting the mother's decision on whether to remain at home or work away from home. One of them is that the opportunities for a woman to find a job within a reasonable distance from home are greater in cities and in industrial centers than in country communities.

Three of the mothers left their employment after the children developed diabetes. Two of the children belong to the GF group and one to the P group. The mothers of the children with Good or Fair Control have remained at home though one of them has seriously considered

returning to work on two different occasions. Each time the child developed ketoacidosis had to be hospitalized. The mother in the case of Poor Control has returned to work away from home.

Stability of the home

A study like this can reveal only the most obvious cases of psychological disruption in the home. The reasons for this are twofold. 1) The number of interviews per family is small and the study is essentially centered around the child and his illness. With these reservations in mind the following results are presented.

All the children seem to have relatively stable homes. All but one child have mother and father living at home. In that one case, belonging to the P group the mother is dead. There is one child in each group whose mother has been previously married.

Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's illness

Table 14 shows the incidence of emotional disturbances and psychosomatic conditions in the parents of the GF group and the P group respectively.

Table 14 Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's diabetes.

	GF	P	Total
Neurotic symptoms in the mother	2	3	5
Depressive state in the mother	1	—	1
Psychosomatic condition in the mother	—	1	1
Neurotic symptoms in the father	1	1	2
Depressive state in the father	1	1	2
Psychosomatic condition in the father	—	1	1
Psychotic episodes in both parents	1	—	1
No known emotional disturbances or psychosomatic conditions	24	23	47
	30	30	60

The incidence of emotional disturbances and psychosomatic conditions in the parents is about the same in the two groups: 6 cases in the GF group and 7 cases in the P group. Of these 13 cases 3 have been hospitalized, 4 have been treated by private physicians and 6 have never sought professional help for their conditions.

The children's emotional health before the onset of diabetes

Table 15 shows the incidence of neurotic and characterological symptoms in the children before the onset of diabetes.

Table 15 Neurotic and characterological symptoms in the children before the onset of diabetes

	GF	P	Total
Enuresis	—	4	4
Encopresis	—	1	1
Enuresis and encopresis	1	—	1
Anxiety state childhood phobia	—	1	1
Behavioral disturbances (defiance, hitting out at once)	1	—	1
	2	6	8

There are considerable differences of opinion in the literature regarding the age at which a child should be labeled enuretic or encopretic. In this study the data obtained by Bellman in Swedish population are used, the age limit for enuresis is 4 years and for encopresis between 3 and 4 years. (8)

Although the figures in Table 15 are far too small for any conclusions, it might be noted that in this series the children who later developed poor control of their diabetes had slightly higher incidence of enuresis at the time of onset of diabetes.

Moreover it is a common observation that some of the more permanent personality disorders are easily overlooked or wrongly interpreted as transient by the parents.

3. The emotional health of the child

Immediate reaction

By means of interviews with parents as well as by observing them during the visiting hours on the ward an attempt was made to learn how the parents reacted to the fact that the child had diabetes. For most of the parents the feeling was bewilderment and even shock, and many felt sad and depressed. In the following the most typical responses of the parents are presented with the inner feelings which, in the author's opinion, they reflected.

Bewilderment and shock As if everything

This is especially true in the case of young children. Because of the significantly earlier age of onset in the P group a greater number of disturbed children belonging to that group may not have been included in the figures.

Emotional stress as a precipitating factor

Table 16 shows the known incidence of different stressful life situations in the cases of the series.

Table 16 Types of stressful life situations

	GF	P	Total
Death of a relative	2	1	3
Starting school	1	1	2
Birth of a sibling	3	1	4
Separation from home	—	1	1
Family move to another locality	—	1	1
Physical injury intrinsically harmless but shocking for the child	—	1	1
Sibling seriously injured in traffic accident	—	1	1
	6	7	13

The cases marked 1 are those where the mother or the child spontaneously connected the event with the onset of the child's diabetes.

As is shown in Table 16, the incidence of stressful life situations prior to diagnosing the child's diabetes is about the same in both diabetic groups.

had stopped. As if blank wall had risen in front of me. "Everything was in confusion."

Anxiety and fears "I myself will be taken to mental hospital." "I am afraid of the insulin injection." "I fear the diet."

Depressive feelings "We were quite down for long time." "We thought he might die in the hospital."

Guilt feelings both realistic and unrealistic, were found in connection with depressive feelings. They were conveyed in the following statements.

Realistic guilt feelings: Mother was working long hours outside of the home and did not have time to take the child to the doctor earlier.

Unrealistic guilt feelings: "The child was breast fed for more than 1½ years, was it

Mothers employment

Of the 60 children included in the study the mothers of 46 worked solely at home. 25 of these 46 children belonged to the GF group and 21 to the P group. The mothers of another 5 children in the GF group and of 6 children in the P group held full time jobs away from home. In another 2 of the P group cases the mothers were working part time outside the home. In the last case the mother of the diabetically poorly controlled child is dead.

Table 13 shows the mothers employment for the GF and the P groups respectively

Table 13 Mothers employment

	GF	P	Total
Housewife	25	21	46
Part time away from home	—	2	2
Full-time away from home	5	6	11
Mother deceased	—	1	1
	30	30	60

The overall incidence of mothers working away from home is 22 % (16 % in the GF group and 28 % in the P group). These figures are relatively low when compared with the overall incidence of married women in gainful employment in Finland. Exact comparative data can be obtained only from the Statistical Bureau of the city of Helsinki where in 1965 56 % of married women were working away from home.

This difference can be partly explained by the fact that our Children's Hospital serves a large number of country communities as well as the city of Turku itself. A high proportion of the population in these communities are farmers. 14 of the diabetics in the series are the children of small farmers and the mothers take an active part in the farm work.

There are of course many other factors affecting the mother's decision on whether to remain at home or work away from home. One of them is that the opportunities for a woman to find a job within a reasonable distance from home are greater in cities and in industrial centers than in country communities.

Three of the mothers left their employment after the children developed diabetes. Two of the children belong to the GF group and one to the P group. The mothers of the children with Good or Fair Control have remained at home though one of them has seriously considered

returning to work on two different occasions. Each time the child developed ketosacidosis and had to be hospitalized. The mother in the case of Poor Control has returned to work away from home.

Stability of the home

A study like this can reveal only the most obvious cases of psychological disruption in the home. The reasons for this are twofold: 1) the number of interviews per family is small and 2) the study is essentially centered around the child and his illness. With these reservations in mind, the following results are presented.

All the children seem to have relatively stable homes. All but one child have mother and father living at home. In that one case, belonging to the P group, the mother is dead. There is one child in each group whose mother has been previously married.

Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's illness

Table 14 shows the incidence of emotional disturbances and psychosomatic conditions in the parents of the GF group and the P group respectively.

Table 14 Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's diabetes.

	GF	P	Total
Neurotic symptoms in the mother	2	3	5
Depressive state in the mother	1	—	1
Psychosomatic condition in the mother	—	1	1
Neurotic symptoms in the father	1	1	2
Depressive state in the father	1	1	2
Psychosomatic condition in the father	—	1	1
Psychotic episodes in both parents	1	—	1
No known emotional disturbances or psychosomatic conditions	24	23	47
	30	30	60

The incidence of emotional disturbances and psychosomatic conditions in the parents is about the same in the two groups: 6 cases in the GF group and 7 cases in the P group. Of these 13 cases 3 have been hospitalized, 4 have been treated by private physicians and 6 have never sought professional help for their conditions.

cases than is possible in a study like this. Two tentative interpretations are therefore offered.

1) In about two thirds (16 out of 24) of the mothers of children who later achieved well or fairly controlled diabetes, the initial insomnia subsided in less than 1 month.

It can be conjectured that the mothers of children in the GF group were able to work through and gain mastery over the initial anxiety and depression more quickly than the mothers of the P group children whose unresolved grief may have been the cause of more persistent insomnia.

2) If the defence mechanism of denial started to operate in the parents' minds quickly after the child's illness was diagnosed, it is possible that the mothers, in denying the difficulties inherent in the situation, also have forgotten short-lived symptoms.

Development of coping devices

External coping devices

In the course of this study it could be seen how the parents, after the initial period of bewilderment, anxiety depression etc. gradually started to adjust to the child's illness. The diabetic regimen became a part of the family's normal daily life. Many mothers expressed this by saying "When one gets to know the illness it becomes less frightening" or "I realized that any child can lead an almost normal life" or "It could be worse. Blind, deaf and crippled children are much worse off". In some instances the parents' anxiety diminished when the child himself took part of the responsibility. The adjustment to the child's illness takes place at two different levels: the parents learn to handle the tasks of the child's illness and at the same time they become able to defend themselves against feelings of anxiety, depression, etc. In other words the parents learn how to handle both the internal and external pressures to which they are exposed by the child's illness. To clarify the individual differences in these adjustment processes and the ways they affect the course of the child's illness are among the aims of the present study.

I this study the terms external coping, coping process and coping device refer to the ways in which the parents handle the arduous — usually

daily — tasks caused by the child's illness. These devices can be grouped into two main categories.

- 1) *Constructive external coping devices*
- 2) *Non-constructive external coping devices*

1) *Constructive external coping devices* The parents show a tolerant and responsible acceptance of the situation. In practical terms, this means that the parents seriously take into account the limitations and requirements imposed by the child's illness, while at the same time they emphasize the normal aspects of the child's life.

2) *Non-constructive coping devices* can be divided into the following subcategories

a) *Poor co-operation in dietary regimen* the parents fail to provide the child with an adequate diabetic diet (sugar free, low in carbohydrates and fat, rich in protein) because they do not really believe it necessary for the child.

b) *Poor co-operation in medical check-ups* the parents neglect the regular medical care of their diabetic child, failing to bring him for regular visits to the out-patient department.

c) *Helplessness about dietary regimen* becoming evident in three different ways.

— the child refuses to eat the prescribed diet and the mother accedes to this through passive resignation and freely giving the child unsuitable food, usually carbohydrate and fat,

— the child buys sweets with his pocket money every day on his way to or from school and the parents fail to prevent it,

— often the school cook regularly "forgets" to prepare suitable food for the diabetic.

d) *Helplessness about insulin injections* The parent is so insecure, helpless or phobic that he cannot give the insulin injections. There are only

few helpless families in this regard in this series if one parent is unable to give the injections the other usually takes the responsibility. There may be more helpless fathers than is indicated by the figures below if the mother is capable of handling this situation adequately the family is not rated as a helpless family.

The parents may be helpless in more than one area of diabetic care; in these instances they are rated according to the area which seems to cause the greatest difficulty in the child's daily care.

because of that he developed diabetes? "Father was sick with a heart condition at the time the child was conceived could this cause his diabetes? "Perhaps I gave him too many sweets. I was never given sweets in my childhood and I thought I would make it up to my children. The guilt feelings are also clearly revealed in questions like "Why did it happen to us? What had I done to deserve this punishment?"

Aggression In some instances the child's illness apparently brought out aggressive feelings in the parent towards the child "It would be better if the child were to die than remain sick. In other instances the aggressive feelings were directed towards the hospital personnel, who were accused and berated.

Wishful thinking In some instances the parents consoled themselves with wishful thinking, usually imagining that the diagnosis of diabetes was mistaken or that the diabetes could be totally cured. Perhaps it is a mistake. It can only be a temporary upset. There must be some place in the world where diabetic children are treated without insulin. "Do diabetics have a bracelet to indicate the level of the blood sugar?"

Table 17 lists the immediate reactions of the parents of children in the GF and P groups respectively. It also shows the incidence of the immediate feelings and reactions of the parents.

Table 17 Immediate reactions of parents

	GF	P
Bewilderment shock	17	16
Anxiety fears hysterical behavior		
phobic symptoms	21	22
Insomnia	24	11
Depressive feelings realistic and		
unrealistic guilt feelings	24	19
Aggression towards the child or		
the hospital personnel	1	1
Wishful thinking	7	1

Two mothers sought medical help for their own conditions during the initial stage of the child's illness.

In the initial stages of the study the author was impressed by the fact that some of the very parents whose immediate behavior was most

anxious fearful depressed and even disorganized had been able in the course of a few weeks to make an adequate adjustment, both externally and internally as it were, to the child's illness. As the study progressed and when all the data were gathered it became evident that those first few parents had not been exceptions. On the contrary as is shown in Table 17 the frequency of initial bewilderment or shock, anxiety fears, hysterical and phobic symptoms as well as depressive feelings was about the same in the parents of both groups. The differences were mainly in the following areas.

1) *Initial insomnia* was about twice as common in the parents (usually mothers) of what later became the GF cases.

2) *Wishful thinking* was also more common in the mothers of the GF group.

The overall picture of the immediate reactions is much more emotional vivid and colorful in the mothers of the GF group than in those of the P group.

The reason for this can not be stated for certain. It can be hypothesized however that from the very beginning the parents of the P group have denied that strong emotions were aroused by the situation. As will be pointed out later the defence mechanism of denial plays a prominent role in the later adjustment of parents of the P group to their child's illness.

Table 18 shows the duration of initial insomnia in parents of the subsequently GF and P cases respectively.

Table 18 Duration of insomnia

	GF	P
Less than 1 week	10	1
1 week to 1 mo	6	2
1 mo to 6 mo	3	4
6 mos to 1 yr	1	—
More than 1 yr	2	4
	24	11

The figures are too small to be evaluated statistically. Nevertheless from these figures one gains the impression that in the parents of the GF group the insomnia tended to subside more quickly than in the parents of the P group. Again the reason for this is unknown and could be convincingly revealed only by a much more detailed scrutiny of individual

comes then is possible in a study like this. Two tentative interpretations are therefore offered

1) In about two thirds (16 out of 24) of the mothers of children who later achieved well or fairly controlled diabetes, the initial insomnia subsided in less than 1 month.

It can be conjectured that the mothers of children in the GF group were able to work through and gain mastery over the initial anxiety and depression more quickly than the mothers of the P group children whose unresolved grief may have been the cause of more persistent insomnia.

2) If the defence mechanism of denial started to operate in the parents' minds quickly after the child's illness was diagnosed, it is possible that the mothers, in denying the difficulties inherent in the situation, also have forgotten short-lived symptoms.

Development of coping devices

External coping devices.

In the course of this study it could be seen how the parents, after the initial period of bewilderment, anxiety depression etc., gradually started to adjust to the child's illness. The diabetic regimen became a part of the family's normal daily life. Many mothers expressed this by saying "When one gets to know the illness, it becomes less frightening" or "I realized that my child can lead an almost normal life" or

"It could be worse. Blind, deaf and crippled children are much worse off". In some instances the parents' anxiety diminished when the child himself took part of the responsibility. The adjustment to the child's illness takes place at two different levels: the parents learn to handle the tasks of the child's illness and at the same time they become able to defend themselves against feelings of anxiety, depression, etc. In other words the parents learn how to handle both the internal and external pressures to which they are exposed by the child's illness. To clarify the individual differences in these adjustment processes and the way they affect the course of the child's illness are among the aims of the present study.

In this study the terms *external coping*, *coping process* and *coping device* refer to the way in which the parents handle the various — usually

daily — tasks caused by the child's illness. These devices can be grouped into two main categories:

- 1) *Constructive external coping devices* and
- 2) *Non-constructive external coping devices*

1) *Constructive external coping devices*: The parents show a tolerant and responsible acceptance of the situation. In practical terms, this means that the parents seriously take into account the limitations and requirements imposed by the child's illness, while at the same time they emphasize the normal aspects of the child's life.

2) *Non-constructive coping devices* can be divided into the following subcategories:

a) *Poor co-operation in dietary regimen*: the parents fail to provide the child with an adequate diabetic diet (sugar free, low in carbohydrates and fat, rich in protein) because they do not really believe it necessary for the child.

b) *Poor co-operation in medical check-ups*: the parents neglect the regular medical care of their diabetic child, failing to bring him for regular visits to the out-patient department.

c) *Helplessness about dietary regimen* becoming evident in three different ways.

— the child refuses to eat the prescribed diet and the mother accedes to this through passive resignation and freely giving the child unsuitable food, usually carbohydrate and fat.

— the child buys sweets with his pocket money every day on his way to or from school and the parents fail to prevent it.

— often the school cook regularly forgets to prepare suitable food for the diabetic.

d) *Helplessness about insulin injections*: The parent is so insecure, helpless or phobic that he cannot give the insulin injections. There are only a few helpless families in this regard in this series. If one parent is unable to give the injections, the other usually takes the responsibility. There may be more helpless fathers than is indicated by the figures below if the mother is capable of handling this situation adequately the family is not rated as a helpless family.

The parents may be helpless in more than one area of diabetic care; in these instances they are rated according to the area which seems to cause the greatest difficulty in the child's daily care.

Table 19 shows the distribution of different external coping devices in the parents in the GF and P groups respectively

Table 19 *External coping devices*

	GF	P	Total
Constructive coping	25	5	30
Non-constructive coping	5	25	30
a) poor co-operation in dietary regimen	(2)	(13)	(15)
b) poor co-operation in medical check ups	(1)	(2)	(3)
c) helplessness about dietary regimen	(1)	(8)	(9)
d) helplessness about insulin injections	(1)	(2)	(3)
	30	30	60

As is shown in Table 19 the constructive coping devices were much more common in the GF group (25 cases) than in the P group (5 cases). On the other hand helplessness and poor co-operation were frequent findings in the P group (25 cases) as compared with the 5 cases in the GF group. These differences are statistically significant ($p < 0.001$).

One of the main areas where the family's coping with the child's illness can be observed is the handling of the *diabetic dietary regimen*. This is shown in Table 20.

Table 20 *The child's diet*

	GF	P	Total
Sugar free - low in carbohydrates and fat - rich in protein	19	7	26
Excess in carbohydrates (bread and potatoes) daily or several times a week	3	4	7
once a week — once a month	1	—	1
Excess of fat daily or several times a week	1	3	4
once a week — once a month	—	1	1
Free diet without sugar	—	9	9
Deserts, candies etc. daily or several times a week	4	3	7
once a week — once a month	2	1	3
No dietary restrictions	—	2	2
	30	30	60

Eleven families in the GF group have adopted the child's diet abandoning sugar and cutting down on fat. In two other families where the

other members of the family have no dietary restrictions the mother has given special attention to the child's diet attending courses, reading literature, etc. Such phenomena have no occurred in the families of the P group.

The decision of the family to keep to a diet which is suitable for their diabetic child requires good co-operation from all the members of the family. An example of this is a mother who relates the following episode: "When I came home, after our child's diabetes had been confirmed my husband made the decision for us all. He said that we were all going to follow the child's diet." Thus of course, requires an empathetic relationship toward the sick child. The following example may serve as an illustration of an entirely different reaction to the child's diet: The mother of a poorly controlled child said that when she came home, after the child's diabetes had been diagnosed the father took the sugar bowl away from the coffee table, the mother put it back on the table, insisting that it should remain there. "By every means I have tried not to pay too much attention to the child's illness."

Daily insulin injections form another important area where the coping devices of the parents can be seen. Table 21 shows who is the person giving the insulin injections in the families of the GF and the P groups respectively.

Table 21 *Person(s) who give the daily insulin injections*

	GF	P	Total
Mother	14	17	31
Father	2	6	8
Mr, her and child in turn	11	3	14
Father and child in turn	—	2	2
Mother and father in turn	3	2	5
	30	30	60

There are 16 families in the GF group in which only one member either mother or father gives the daily insulin injections as compared with 23 such families in the P group. Further there are twice as many families (14) in the GF group where the members take turns in giving the daily insulin injections as compared with 7 families in the P group. The difference is statistically almost significant ($p < 0.10$). The most probable explanation for this is that in the GF group the members of the family experience diabetic care as a common responsibility.

Internal coping devices

In this study the terms internal coping, internal coping process and internal coping device refer to the various maneuvers which the parents use to avoid the feelings of anxiety. Internal coping is a silent one (= unconscious) operation but manifests itself in the person's words and actions. Of many possible coping devices, each individual tends to rely on a few which then become characteristic for him.

The following internal coping devices were observed operating in the parents of the cases under study:

1) Many parents were able to admit to feelings of anxiety, loss and depression and at the same time were able to control them adequately. In many instances the parents find some enjoyment in caring for the sick child. In this way they have channeled their anxiety into socially valuable and rewarding behavior. This coping device comes close to the concept of sublimation which in earlier psychoanalytic writings has been viewed as one of the mature defence mechanisms.

On the other hand, Kubie has shown how the concept of sublimation in the hands of various authors has implied many different things, no two authors being consistent. For this reason among others Kubie recommends that the concept be discarded (84).

2) Some parents were apparently unable to admit the painful feelings aroused by their child's illness. They tended to deny them. Both external events and internal feelings can be denied. The denial of external events implicitly means that the internal pain is also denied.

A few examples of parents' statements might be quoted: "I have no sick child." "The doctor told me this my child is serious case but I cannot regard him as such. A cold, the head is a little diabetes."

3) In some cases the denial of feeling of helplessness apparently leads to an omnipotent attitude regarding the care of the diabetic child. The parents usually the mother think that they know everything about the diabetic regimen, more than the medical personnel. The rationalization behind this is their feeling that because they have taken care of the diabetic child 4 hours a day for so many years, they must know more about the disease than those whose knowledge is based on books and short term care of the child in the hospital. "Of course, the doctor's knowledge doesn't do me any harm," one of the mothers remarked. In simpler

form, the omnipotent attitude comes out in a statement like the following (by a mother of a poorly controlled child): "My child is the best treated diabetic in the whole vicinity." Omnipotent thinking closely resembles the defence mechanism which is known as reaction formation. This is a mechanism whereby one of a pair of ambivalent attitudes (e.g. helplessness and omnipotence) is repressed and kept unconscious by overemphasis on the other. Fuchs and Hess who observed the parents of 17 children with ulcerative colitis, reached conclusions very similar to those described above. They reported that in all their cases the mother appeared dominating and over-controlling toward the patient. The mothers consciously demonstrated extreme though superficial concern for the child, but in many cases the mother's negative attitude was shown in her apparent need for illness in the child (43).

4) Some parents had feelings of being permanently helpless, impotent, and resigned in the face of the painful situation caused by the child's illness. In this study the term depression is used to describe this kind of affective response according to Sandler and Joffe's description.

Its core is a basic depressive-affective response, but it includes as well a number of features which may be understood as representing attempts to deal with the existence of this affect or directed towards preventing its emergence. In particular because of the important role which undischarged aggression plays in the genesis of the depressive response, we find derivatives of or defences against aggressive manifestations also complicating the picture. The depressive reaction, considered as a basic affective state, may like anxiety be of long or short duration, of low or high intensity and it can occur in a wide variety of personality types and clinical conditions. It can occur at any developmental stage and is found in association with obsessions, phobias, etc. (116).

5) The experiencing of mental pain normally mobilizes aggression which is then directed against what is felt to be the source of the pain. There are several cases in the series where the parent's aggression apparently was felt against the sick child. This can be exemplified by a statement of a mother: "I once read in a newspaper about a mother who had hidden her child in a closet for many years. My friends were horrified when they read it, but I can understand that mother. I find it difficult to walk on the streets with my sick child."

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances. This is a defence mechanism which shifts the goal of the danger of the alarming impulse by attributing the affect (in this case aggression) to some other cause.

6) In phobias the person's own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety. The resulting phobia usually involved insulin injections.

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respectively.

Table 22 External and internal coping devices in the GF group

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med. check-ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins. inj						1	1
	19	4		4	2	1	30

Table 23 External and internal coping devices in the P group

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			5
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med. check-ups		1		1			2
Helplessness in dietary regimen		2		3	1		6
Helplessness in ins. inj		1		1			2
	3	11	4	10	2		30

As can be seen from the above tables the parent's ability to cope with the demands made upon them by their child's illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety, loss and depression which they experience in the first stages of the child's illness.

The ability to face the feelings of anxiety etc. and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping. On the contrary denial, omnipotent thinking and persistent depression are more often related to the non-constructive external coping.

4 The child's reaction to the diabetes

Immediate reactions

The child's immediate reaction to the discovery of diabetes in himself could be evaluated only in those cases where the child's first hospitalization occurred at the time the study took place. There were 17 such cases among the series of 60. In additional 3 cases either the mother or the hospital record provided sufficient data for making an evaluation.

The immediate reactions are shown in Table 24.

Table 24 The immediate reaction in children

Type of reaction	GF	P	Total
Anxiety reactions	10		10
Hysterical paralysis	1		1
Depressive reaction	4		4
Smiling depression		1	1
Suicidal threats		1	1
Aggression towards the illness or the mother	2		2
No disturbances	1		1
	18		20

The figures in Table 24 are too small for detailed comparison. In addition to this one has to bear in mind that the child's reaction to the illness in many instances cannot be distinguished from his reaction to the hospitalization. A number of clinical and experimental studies on the emotional implications of hospitalization the main foci of anxiety have been found to be

a) separation from the parents and exposure to the unfamiliar hospital surroundings and

b) fear of diagnostic and treatment procedures.

Age was an important determinant of which could be more difficult for the child. Anxiety about hospitalization and separation was greatest in the youngest children (72, 109).

Something can, however, be said about the figures in Table 24.

1) the severity of the child's immediate reaction, especially the amount of anxiety displayed, does not seem to be related to the later controllability of his diabetes. Even the very seriously disturbed child, the girl with hysterical paralysis recovered emotionally in the course of

a few weeks, and, at least during the subsequent three years has been a well controlled diabetic.

b) The term "Smiling depression" was introduced by Toolan in the following words: "Boys especially have a need to hide their true feelings, particularly any soft tender weak sentiments. At times a teenager may deliberately mask his true feelings by a pretence of happiness and exhibit the picture of smiling depression." (142) Figures 6 and 7 (page 34) illustrate this. A patient in this series, a boy of 13 made a drawing while on the ward (Figure 6) and another drawing (Figure 7) on the same day as the psychiatric interview. The drawing made on the ward is an artificially gay one while the drawing made during the psychiatric interview is rather sad and empty. This particular instance came to the author's notice because the boy's first hospitalization took place during the collection of this study material. It can be hypothesized that this kind of reaction may be more common than is realized but difficult to trace because of the pretence of happiness.

Later adjustment

The psychiatric assessment of the child at the final stage of the study was based on three main sources of information.

- 1) data from interviews with the parents
- 2) the author's evaluation of the child, based on interviews or play observations
- 3) the teacher's evaluation of the child's social adjustment at school.

If the child was hospitalized at the time this study took place the occupational therapist's weekly reports, as well as the observations of the ward personnel have also been used as additional sources of information.

Table 25 shows the list of symptomatic reactions displayed by the children in the GF and P groups respectively. The reactions have been grouped into five main categories and several subcategories.

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances. This is a defence mechanism which shifts the goal of the danger of the alarming impulse by attributing the affect (in this case, aggression) to some other cause.

6) In phobias the person's own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety. The resulting phobia usually involved insulin injections.

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respectively.

Table 22 *External and internal coping devices in the GF group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med. check ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins. inj						1	1
	19	4		4	2	1	30

Table 23 *External and internal coping devices in the P group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			5
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med. check-ups		1		1			2
Helplessness in dietary regimen		2		5	1		8
Helplessness in ins inj		1		1			2
	3	11	4	10	2		30

As can be seen from the above tables the parent's ability to cope with the demands made upon them by their child's illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety loss and depression which they experience in the first stages of the child's illness.

The ability to face the feelings of anxiety etc. and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping. On the contrary denial omnipotent thinking and persistent depression are more often related to the non-constructive external coping.

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Table 24 The immediate reactions in children

Type of reaction	GF	P	Total
Anxiety reactions	10		10
Hysterical psychosis	1		1
Depressive reaction	4		4
"Smiling depression"		1	1
Suicidal threats		1	1
Aggression towards the illness or the mother	2		2
No disturbances	1		1
	18	2	20

The figures in Table 24 are too small for detailed comparison. In addition to this, one has to bear in mind that the child's reaction to the illness in many instances cannot be distinguished from his reaction to the hospitalization. In number of clinical and experimental studies on the emotional implications of hospitalization the main foci of anxiety have been found to be

- 1) separation from the parents and exposure to be unfamiliar hospital surroundings, and
 - 2) fear of diagnostic and treatment procedures.
- Age was an important determinant of which could be more difficult for the child. Anxiety about hospitalization and separation was greatest in the youngest children (72, 109).

Something can, however, be said about the figures in Table 24.

1) the severity of the child's immediate reaction especially the amount of anxiety displayed does not seem to be related to the later controllability of his diabetes. Even the very seriously disturbed child, the girl with hysterical psychosis recovered emotionally in the course of

a few weeks and, at least during the subsequent three years, has been a well controlled diabetic.

6) The term "Smiling depression" was introduced by Toolan in the following words: "Boys especially have need to hide their true feelings, particularly any soft, tender weak sentiments. At times a teenager may deliberately mask his true feelings by a pretence of happiness and exhibit the picture of a smiling depression." (142) Figures 6 and 7 (page 54) illustrate this. A patient in this series a boy of 13 made a drawing while on the ward (Figure 6) and another drawing (Figure 7) on the same day as the psychiatric interview. The drawing made on the ward is an artificially gay one while the drawing made during the psychiatric interview is rather sad and empty. This particular instance came to the author's notice because the boy's first hospitalization took place during the collection of this study material. It can be hypothesized that this kind of reaction may be more common than is realized but difficult to trace because of the pretence of happiness.

Later adjustment

The psychiatric assessment of the child at the final stage of the study was based on three main sources of information:

- 1) data from interviews with the parents
- 2) the author's evaluation of the child, based on interviews or play observations
- 3) the teacher's evaluation of the child's social adjustment at school.

If the child was hospitalized at the time this study took place, the occupational therapists' weekly reports, as well as the observations of the ward personnel, have also been used as additional sources of information.

Table 25 shows the list of symptomatic reactions displayed by the children in the GF and P groups respectively. The reactions have been grouped into five main categories and several subcategories.

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances. This is a defence mechanism which shifts the goal of the danger of the alarming impulse by attributing the affect (in this case aggression) to some other cause.

6) In phobias the person's own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety. The resulting phobia usually involved insulin injections.

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respectively.

Table 22 *External and internal coping devices in the GF group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med. check ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins. inj						1	1
	19	4		4	2	1	30

Table 23 *External and internal coping devices in the P group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			5
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med. check-ups		1		1			2
Helplessness in dietary regimen		2		5	1		8
Helplessness in ins. inj		1		1			2
	3	11	4	10	2		30

As can be seen from the above tables the parent's ability to cope with the demands made upon them by their child's illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety loss and depression which they experience in the first stages of the child's illness.

The ability to face the feelings of anxiety etc. and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping. On the contrary denial omnipotent thinking and persistent depression are more often related to the non-constructive external coping.

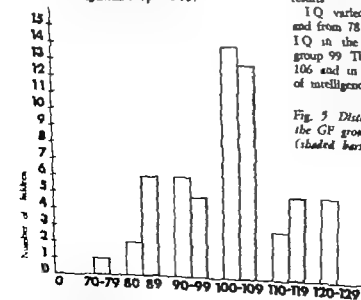
4 The child was rated as having a *personality trait disorder* if the behavioral difficulties had become fixed patterns which the child carried over into all situations. In contrast to psychoneurosis, the personality trait disorders are more pervasive; there is not even the marginal healthy living a psychoneurotic child can have.

Table 26 shows the distribution of the above-mentioned psychiatric diagnostic categories in the GF and the P groups respectively.

Diagnosis	GF	P	Total
Normal adjustment	11	4	15
Mild adjustment disorder	8	8	16
Psychoneurosis	8	4	12
Personality trait disorder	3	14	17
	30	30	60

As can be seen from Table 26 in the categories of normal adjustment and psychoneurosis the GF cases outnumber the P cases, whereas the personality trait disorders, in other words the more difficult emotional disturbances, are more frequent in the P group than in the GF group.

When, in the statistical evaluation, normal adjustment and mild adjustment disorder were combined, and, similarly psychoneurosis and personality trait disorder, it was discovered that normal adjustment and mild adjustment disorder were more frequent in the GF group than in the P group. Accordingly psychoneurosis and personality trait disorder were more frequently found in the P group. The difference is statistically almost significant ($p < 0.10$).



School achievement

The child's school achievement is based upon the teacher's evaluation. The teacher was asked to rate the child's achievement as above average, average or below average as compared with the average achievement of the class. The results are shown in Table 27.

Table 27 School achievement

	GF	P	Total
Above average	11	5	16
Average	9	10	19
Below average	4	10	14
	24	25	49

The remaining 11 children have either left school or not yet entered school.

6 children in the P group have had to repeat class one of them twice. None of those in the GF group has repeated a class. As can be seen from Table 27 one third of the P cases are at the bottom of the academic achievement scale, while one third of the GF cases are at top of the academic achievement scale. The difference is statistically almost significant ($p < 0.10$).

Psychological data

Intelligence test

The T.M.L. intelligence test was given to all diabetic children in the study with the following results.

I.Q. varied from 80 to 127 in the GF group and from 78 to 119 in the P group. The average I.Q. in the GF group was 102 and in the P group 99. The median I.Q. in the GF group was 106 and in the P group 100. The distribution of intelligence quotients is shown in Fig. 3.

Fig. 3 Distribution of intelligence quotients in the GF group (white bars) and in the P group (shaded bars)

Table 25 List of symptomatic reactions

	GF	P	Total
A Disturbances related to Bodily Functions			
1 Sleeping			
Difficulty in falling asleep	2	1	3
Restless sleep	1	4	5
Night fears	1		1
2 Bladder Function			
Enuresis (nocturnal)	5	8	13
3 Speech and language			
Elective mutism		2	2
Infantile speech		1	1
Stuttering		1	1
4 Motor Patterns			
Hyperactivity	1	3	4
Passivity	1		1
Tics	1		1
B Developmental Difficulties			
1 Excessive separation anxiety		1	1
2 Problems in sexual identification		1	1
C. Disturbances in Social Behavior			
1 Aggressive Behavior	1	3	4
2 Antisocial Behavior			
Stealing		1	1
Lying		2	2
3 Oppositional Behavior			
Passive resistance		9	9
Passive-aggressive behavior		1	1
Disobedience		1	1
Running away		1	1
4 Isolated Behavior			
Withdrawal	2	4	6
Autistic behavior		1	1
5 Problems in Dependency —			
Independency			1
Clinging behavior	1		1
D Disturbances in Affective Behavior			
1 Manifest anxiety			
Anxiety attacks	3	5	8
Free floating anxiety	7	1	8
Uncontrollable crying screaming	2	4	6
2 Manifestly Fearful Behavior			
Specific fears	5	1	6
3 Manifest Depression			
Depressive episodes	1	1	2
Chronic depression		3	3
Feelings of inadequacy inferiority	4	5	9

E. Difficulties in Integrative Behavior	GF	P	Total
1 Impulsive Behavior	1	2	3
2 Limited Tolerance of Frustration	1	1	2
3 Over use of Adaptive Mechanisms			
Over strenuous denial		1	1
Marked projection	1	1	2
Over-concern with cleanliness		1	1
Obsessive rumination		1	1
	41	72	113

Number of symptomatic reactions

In this study the children in the P group had more symptomatic reactions than the children in the GF group. The number of symptomatic reactions per child was 1.3 in the GF group and 2.4 in the P group.

Quality of symptomatic reactions

When, in statistical analysis the Disturbances related to Bodily Functions, Developmental Difficulties and Disturbances in Social Behavior were combined and, correspondingly Disturbances in Affective Behavior and Difficulties in Integrative Behavior were combined, it was found that the differences between the GF and P groups were mainly in the areas of Bodily Functions, Personality Development and Social Behavior the children in the P group having a significantly greater number of disturbances ($p < 0.02$).

Difficulties in Affective and Integrative Behavior were equally frequent in the two groups.

When finally the child's adjustment was evaluated the following criteria were used:

1 The child was rated as having made a *normal adjustment* if he displayed none of the symptoms listed above and if all three sources of information indicated age-appropriate behavior.

2 The child was rated as having a *mild adjustment disorder* if one of the three main sources of information, parents, school or the examination indicated disturbed behavior in the form of the symptomatic reactions listed above.

3 The child was rated as having a *psychoneurosis* if at least two of the sources of information indicated signs of anxiety or depression or if the child had clear-cut phobic or hysterical symptoms.

There is no statistically significant difference between the two diabetic groups

Impulsiveness

GF	$\approx 24.8 \%$
	$\approx 24.4 \%$
t	≈ 0.033
p	> 0.10

The difference between the two diabetic groups in terms of their Impulsiveness is even smaller than of their Extrapuniveness or Inopuniveness. The children in the two diabetic groups show equal tendencies to avoid and hide their aggressions evenly

Reaction Types

Obstacle Domination

GF	$\approx 26.4 \%$
P	$\approx 28.3 \%$
t	≈ 0.136
p	> 0.10

Again the difference is so small that t has no statistical significance

Ego-defensive

GF	$\approx 31.8 \%$
P	$\approx 29.8 \%$
t	≈ 0.122
p	> 0.10

The difference is not statistically significant

Need persistence

GF	$\approx 23.3 \%$
P	$\approx 22.6 \%$
t	≈ 0.078
p	> 0.10

The difference between the two groups in terms of Need-Persistence variable is even smaller than in other instances

A summary of responses to the Rosenzweig Picture Frustr. on Test I can be said that no statistically significant differences could be observed between the children in the two diabetic group

The result of the comparison between the diabetic children and normal control subjects

As is indicated also the normative data were obtained mainly from Rosenzweig's study of 256 children from 4 to 13 years of age and on Takala study of Finnish children

The results for each diabetic group are compared with Rosenzweig data

Directions of Aggression

Extrapuniveness

GF	$\approx 38.4 \%$	$t \approx 1.041$	$p > 0.10$
P	$\approx 36.8 \%$	$t \approx 0.746$	$p > 0.10$

Normal group $\approx 48.2 \%$

The children in each diabetic group give more overtly aggressive responses to the Rosenzweig P-F Study. The difference between the GF group and the Normal group is greater than between the P group and the Normal group. However the differences are not statistically significant. The above mentioned differences may be partly due to cultural features. Takala has found that the number of Extrapunitive responses of Finnish children exceed the Rosenzweig norms by 10 % in each age group. When this is taken into account, the figures would be as follows

GF	$\approx 38.4 \%$
P	$\approx 36.8 \%$

Normal group

(Finnish)

$\approx 38.2 \%$

Thus the GF group would come closer to the Normal group of Finnish children than the P group would do.

Inopuniveness

GF	$\approx 16.8 \%$	$t \approx 0.973$	$p > 0.10$
P	$\approx 18.8 \%$	$t \approx 0.634$	$p > 0.10$
Normal group	$\approx 24.1 \%$		

The children in each diabetic group give fewer responses, indicating that they turn aggression on themselves than the children in the Normal group do. The difference between the GF group and the Normal group is greater than between the P group and the Normal group. Even the greater difference is not statistically significant.

Impulsiveness

the GF group	$\approx 24.8 \%$	$t \approx 0.081$	$p > 0.10$
the P group	$\approx 24.4 \%$	$t \approx 0.119$	$p > 0.10$
Normal group	$\approx 25.5 \%$		

The children in each diabetic group give only slightly fewer responses to the Rosenzweig P-F Study than do not blame anyone. The differences are far from having statistical significance

The results broken down into three levels of intelligence are shown in Table 28

Table 28 Level of intelligence in the GF group and in the P group

IQ	GF	P	Total
Over 115 (above normal)	6	2	8
85—115 (normal)	23	23	46
Under 85 (below normal)	1	4	5
No result		1	1
	30	30	60

As can be seen from Table 28 one child in the P group is without result in the intelligence test. This is a girl of 12 who refused to participate in the psychological testing.

Statistical analysis shows that there is no significant difference in the intelligence between the children in the GF and the P group.

Tb Rosenzweig Picture Frustration Test

The Rosenzweig Picture Frustration Test children's form consists of a booklet containing 24 cartoon-like drawings. In each drawing is a person either frustrating a child or insistently pointing out improper behavior on the part of a child. The remarks of the frustrator are indicated whereas the child's responses are not given. The child is requested to tell what he feels would be an appropriate answer.

The responses for each test situation were analyzed in terms of the direction of aggression and of types of reaction to frustration. Each of these categories included three variables. The response categories are presented in Table 29.

Table 29 Rosenzweig Picture-Frustration Test Variables

Directions of Aggression	E Extrapunitiveness	Child turns aggression onto the environment
	I Intropunitiveness	Child turns aggression onto himself; blames or accuses himself. He willingly accepts blame and appears apologetic.
	M Impunitiveness	Aggression is glossed over and evaded. Aggression does not appear in the response.
Reaction Types	OD Obstacle-dominance	The frustrating barrier is outstanding in the response.
	ED Ego-defensive	Personalities of the actors, especially the frustrated child, dominate the response.
	NP Need-persistence	Solution of frustrating problem is emphasized in the responses.

The two diabetic groups (the GF group and the P group) were compared on the basis of the scores on each variable. In addition to this the diabetic groups were compared with normative data reported by Rosenzweig and Takala (115-137).

One child in the GF group and three children in the P group refused to co-operate in the Rosenzweig Picture Frustration test. Thus 29 test protocols were obtained from the GF group and 27 from the P group.

The results of the comparison between the two diabetic groups

Directions of Aggression

Extrapunitiveness

GF	= 58.4 %
P	= 56.8 %
t	= 0.118
p	> 0.10

There is no statistically significant difference between the two diabetic groups.

Intropunitiveness

GF	= 16.8 %
P	= 18.8 %
t	= 0.033
p	> 0.10

There is no statistically significant difference between the two diabetic groups.

Impunitiveness

GF	$\approx 24.8 \%$
	$\approx 24.4 \%$
t	≈ 0.033
p	> 0.10

The difference between the two diabetic groups in terms of their Impunitiveness is even smaller than of their Extrapunitiveness or Intrapunitiveness. The children in the two diabetic groups show equal tendencies to avoid and hide their aggressions evenly.

Reaction Types

Obstacle-Dominance

GF	$\approx 26.4 \%$
P	$\approx 28.3 \%$
t	≈ 0.136
p	> 0.10

Again the difference is so small that it has no statistical significance.

Ego defensive

GF	$\approx 31.8 \%$
P	$\approx 29.8 \%$
t	≈ 0.122
p	> 0.10

The difference is not statistically significant.

Need-persistence

GF	$\approx 23.5 \%$
P	$\approx 22.6 \%$
t	≈ 0.078
p	> 0.10

The difference between the two groups in terms of Need Persistence variable is even smaller than in other measures.

A summary of responses to the Rosenzweig Picture Frustration Test can be said that no statistically significant differences could be observed between the children in the two diabetic group.

For sake of the comparison between the diabetic children and normal control subjects

As indicated also the normative data etc. obtained mainly from Rosenzweig study of 2% children from 4 to 13 years of age and on Takala study of Finnish children.

The results for each diabetic group are compared with Rosenzweig's data.

Directions of Aggression

Extrapunitiveness

GF	$\approx 58.4 \%$	$t \approx 1.041$	$p > 0.10$
P	$\approx 56.8 \%$	$t \approx 0.746$	$p > 0.10$

Normal group

The children in each diabetic group give more overtly aggressive responses to the Rosenzweig P-F Study. The difference between the GF group and the Normal group is greater than between the P group and the Normal group. However the differences are not statistically significant. The above mentioned differences may be partly due to cultural features. Takala has found that the number of Extrapunitive responses of Finnish children exceed the Rosenzweig norms by 10 % in each age group. When this is taken into account, the figures would be as follows:

GF	$\approx 38.4 \%$
P	$\approx 36.8 \%$

Normal group

(Finnish Children) $\approx 38.2 \%$

Thus, the GF group would come closer to the Normal group of Finnish children than the P group would do.

Intrapunitiveness

GF	$\approx 16.8 \%$	$t \approx 0.973$	$p > 0.10$
P	$\approx 18.8 \%$	$t \approx 0.634$	$p > 0.10$

Normal group

The children in each diabetic group give fewer responses indicating that they turn aggression on themselves than the children in the Normal group do. The difference between the GF group and the Normal group is greater than between the P group and the Normal group. Even the greater difference is not statistically significant.

Impunitiveness

the GF group	$\approx 24.8 \%$	$t \approx 0.081$	$p > 0.10$
the P group	$\approx 24.4 \%$	$t \approx 0.119$	$p > 0.10$
Normal group	$\approx 25.5 \%$		

The children in each diabetic group give only slightly fewer responses to the Rosenzweig P-F Study that do not blame anyone. The differences are far from having statistical significance.

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No result		1	1
	30	30	60

As can be seen from Table 28 one child in the P group is without result in the intelligence test. This is a girl of 12 who refused to participate in the psychological testing.

Statistical analysis shows that there is no significant difference in the intelligence between the children in the GF and the P group.

Table 29 Rosenzweig Picture-Frustration Test Variables

Directions of Aggression	E Extrapunitiveness	Child turns aggression onto the environment
	I Intropunitiveness	Child turns aggression onto himself blames or accuses himself. He willingly accepts blame and appears apologetic
	M Impunitiveness	Aggression is glossed over and evaded. Aggression does not appear in the response
Reaction Types	OD Obstacle-dominance	The frustrating barrier is outstanding in the response
	ED Ego-defensive	Personalities of the actors especially the frustrated child dominate the response
	NP Need persistence	Solution of frustrating problem is emphasized in the responses

The two diabetic groups (the GF group and the P group) were compared on the basis of the scores on each variable. In addition to this the diabetic groups were compared with normative data reported by Rosenzweig and Takala (115-137).

One child in the GF group and three children in the P group refused to co-operate in the Rosenzweig Picture Frustration test. Thus 29 test protocols were obtained from the GF group and 27 from the P group.

The results of the comparison between the two diabetic groups

Tb Rosenzweig Picture Frustration Test

The Rosenzweig Picture Frustration Test children's form consists of a booklet containing 24 cartoon-like drawings. In each drawing is a person either frustrating a child or insistently pointing out improper behavior on the part of a child. The remarks of the frustrator are indicated whereas the child's responses are not given. The child is requested to tell what he feels would be an appropriate answer.

The responses for each test situation were analyzed in terms of the direction of aggression and of types of reaction to frustration. Each of these categories included three variables. The response categories are presented in Table 29.

Directions of Aggression

Extrapunitiveness

GF	= 38.4 %
P	= 56.8 %
t	= 0.118
p	> 0.10

There is no statistically significant difference between the two diabetic groups.

Intropunitiveness

GF	= 16.8 %
P	= 18.8 %
t	= 0.033
p	> 0.10

Table 32 shows the Discriminant Function Coefficients obtained arranged in numerical order.

Table 32. Discriminant Function Coefficients.

20.	0.30961	"	1 Integration	0.03402
21.	0.30111		2. Popular	-0.02489
22.	0.29910		3 Movement	-0.01914
23.	0.29825	"	4 Animal	0.01557
24.	0.29488		5 Color	0.01413
25.	0.28988		6. Shading	0.01289
26.	0.28431		7 Barrier	-0.01050
27.	0.28331		8. Hostility	-0.01006
28.	0.25368		9 Space	0.00910
29.	0.25013	P	10 Penetration	0.00875
30.	0.13642		11 Anatomy	0.00817
31.	0.12155		12. Form Appropriateness	-0.00681
32.	0.11979		13 Human	-0.00590
33.	0.08603		14 Reaction Time	-0.00386
34.	0.08312		15 Pathognomonic Verbalization	0.00325
35.	0.07488		16. Rejection	0.00282
36.	0.07327	GF	17 Form Definateness	0.00152
37.	0.07305	P	18 Anxiety	-0.00075
38.	0.07305		19 Location	0.00034
39.	0.07305			
40.	0.07305			
41.	0.07305			
42.	0.06020			
43.	0.06020			
44.	0.05470			
45.	0.04524			
46.	0.02884			
47.	0.02668			
48.	0.02477			
49.	0.02441			
50.	0.01645			
51.	-0.01045			
52.	-0.02332			
53.	-0.02865			
54.	-0.03266			
55.	-0.04326			
56.	-0.05741			
57.	-0.06896			
58.	-0.11030			
59.	-0.12079			
60.	-0.13400			

Three variables, Abstraction, Sex and Balance, are not included in Table 32, because of the infrequency of responses obtained. The greater the absolute value of the discrimination function coefficient of any variable, the more important the variable will be in discriminating between the GF and the P groups. In this material those best discriminative variables are *Integration Popular Movement Animal Color Shading Barrier and Hostility*

From these variables Movement Integration, Popular Barrier and Hostility have proved in number of factor-analytic studies to define the Holzman Factor I which usually accounts for most of the variance. In the same manner the variables Color and Shading define the Factor II. (68) Consequently in this study the best discrimination between the two diabetic groups are the combinations of variables contributing to the Holzman Factors I and II.

According to the interpretation of the factors, the major dimensions measured by these eight variables are as follows.

Factor I Perceptual Maturity and Integrated Ideational Activity

Invariably defined by Movement, Integration, Human, Barrier and Popular Factor I usually

As can be seen from Table 31 the two diabetic groups differ clearly from each other on the Discriminant Line. There is only one exception, a child belonging clinically to the GF group whose Discrimination Points locate him in the middle of the P group

Reaction Types

Obstacle-dominance

GF = 26.4 % $t = 1.150$ $p > 0.10$

P = 28.3 % $t = 1.297$ $p > 0.10$

Normal group = 16.5

The children in each diabetic group give more frustration-oriented responses to the Rosenzweig P.E. Study than the children in the Normal group do. The difference between the GF group and the Normal groups is smaller than between the P group and the Normal group. The differences are not statistically significant.

Ego defensive

GF = 31.3 % $t = 2.740$ $p < 0.01$

P = 29.8 % $t = 2.842$ $p < 0.01$

Normal group = 56.8 %

The personalities of the actors especially the frustrated child dominate the responses of the children in the Normal group more often than in either diabetic group. The differences are statistically significant ($p < 0.01$).

Need-persistence

GF = 23.3 % $t = 0.342$ $p > 0.10$

P = 22.6 % $t = 0.437$ $p > 0.10$

Normal group = 26.4 %

The solution of the frustrating problem is emphasized in the responses of children in the Normal group more often than in either diabetic group. The children in the GF group come closer to the Normal group than the children in the P group do. The differences are not statistically significant.

The only statistically significant difference between the Normal group and the diabetic groups is found in Reaction Types. In frustrating situations the children in the Normal group are more ego-defensive, i.e. more person-oriented than the diabetic children.

The Holtzman Inkblot Technique

The Holtzman Inkblot Technique (HIT) is a new projective method which resembles the Rorschach but differs from it in several respects. Unlike the Rorschach which has ten inkblots, the HIT consists of two parallel forms A and B, each of which contains 45 inkblots constituting the test series plus two practice blots X and Y. The instructions given to the subject emphasize the following points:

1) these inkblots were not made to look like anything in particular

2) different people see different things in each inkblot

3) only one response for each card is desired. The responses are scored in terms of the following 22 variables:

Reaction Time (RT) Rejection (R) Location (L) Space (S) Form Definiteness (FD) Form Appropriateness (FA) Color (C) Shading (Sh) Movement (M) Pathognomonic Verbalization (V) Integration (I) Human (H) Animal (A) Anatomy (At) Abstract (Ab) Anxiety (Ax) Hostility (Hs) Barrier (Br) Penetration (Ph) Balance (B) and Popular (P)

For the analysis of the above mentioned scores the method of *Discrimination Analysis* was used in this study.

The results of the Discrimination Analysis are presented in Tables 30—32.

Table 30 The Mean Values and the Standard Deviations on the Discrimination Line

	GF	P
Mean	0.32603	0.02331
Standard Deviation	0.07243	0.07206

Table 31 shows the Discrimination Points and the Group Rank of each diabetic subject.

Table 31 The Discrimination Point and the Group Rank of each subject.

Group Rank	Discrimination Points	Diabetic Control
1	0.50053	GF
2	0.44840	
3	0.41681	
4	0.39667	
5	0.37545	
6	0.37244	
7	0.36888	
8	0.36459	
9	0.35717	
10	0.34661	
11	0.34016	
12	0.32926	
13	0.32884	
14	0.32289	
15	0.32275	
16	0.31859	
17	0.31236	
18	0.31133	
19	0.30981	

Discussion

The aim of the present study was to discover both the immediate reactions and later adjustment of diabetic children and their parents to the diagnosis of the disease. A special endeavor was made to detect any possible correlations between the various coping processes and the degree of diabetic control.

The reported results concern mainly the GF group in relation to the P group.

1 *Average age at diagnosis of diabetes* was significantly higher in the GF group than in the P group. In the cases included in this material, all the children who had developed diabetes prior to the age of three had poor control of their disease.

2 *The duration of the illness* in the GF group was significantly shorter than in the P group.

3 In the series diabetes was *evenly distributed among males and females* in both the GF group and the P group.

4 Studies of childhood diabetes have clearly demonstrated that diabetes is *recurrent hereditary disease* 20% of the juvenile diabetic having known diabetic relatives at the time of the diagnosis of this disease. In this series 37 of the 60 diabetic children (63%) had relatives known to be diabetic at the time when the whole series had been collected.

The high percentage of diabetic relatives in this series can be explained at least partly by the facts that between the time of the first diagnosis and the last examination 1) new cases of diabetes manifested among the child relatives and 2) cases of diabetes among more distant perhaps already deceased relatives came to the parents' knowledge.

Björkstén and co-workers in their review of the available data concerning the hereditary transmission of diabetes come to the conclusion that the clinically prominent diabetes has a reliable genetic ground and they support the hypothesis of multifactorial heredity. According to their opinion it is probable that the *main* gene affects the islet function and is conveyed by means of an *intermittent* inherited process. The additional

genes could act in promoting the passage from a prediabetic status to latent or clear diabetes. This passage is conditioned by environmental factors too (11).

5 Much has been written about the *growth of diabetic children*. Many authors remarked that height was above normal at the time of diagnosis (44-57). As for ultimate adult stature, most studies over the past twenty-five years indicate that the average heights of both diabetic sexes are below normal, probably because of uniform presence of those 5 to 10 per cent with stunted growth. Knowles and co-workers observed that men and women diabetics were two and one tenth, and one and one-tenth inches respectively shorter than their normal controls. Decrease in stature was mainly in those with diabetes diagnosed before the growthspurt years. (81).

Larsson and Sterky pointed out that in their Swedish study of juvenile diabetics who had reached adulthood, in 12.9 per cent of men and 33 per cent of women the height was below the lower normal limit. No explanation was found for the tendency towards short stature of these patients. They did not deviate from the rest of the cases with regard to age at onset, duration, chronological age, food habits, blood sugar level, insulin requirements or extent of vascular damage. (88).

The presence of stunted growth at the time of last examination in this series is 13.3% (33%) in the GF group and 23.3% in the P group).

The figures are too small for statistical evaluation. Moreover they cannot be considered as final because the majority of the have not yet reached adult stature. A tendency is, however, for the heights to be below the lower normal limit more often in the P group than in the GF group.

6 Swift and co-workers found that the *birth rank* of the childhood diabetic was significantly associated with the diabetic control. In their sample, in contrast to the present study, the eldest child in the family had significantly worse control than did children of other birth rank (135). According to the findings of this study

accounts for more variance than the other. Anxiety and Hostility may also have moderately high loadings on Factor I, particularly among children. A high amount of this factor would be indicative of well organized ideational activity, good imaginative capacity, well differentiated ego boundaries, and awareness of conventional concepts.

Factor II: Perceptual Sensitivity

Defined primarily by Color and Shading, this factor involves sensitivity to the stimulus qualities of the blobs. Reactions to Color or Shading are

indicators of affective responsiveness and not fantasy life.

To summarize, the children in the GF group, according to the HIT results, have more integrated, more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts.

In addition, the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group.

Discussion

The aim of the present study was to discover both the immediate reactions and later adjustment of diabetic children and their parents to the diagnosis of the disease. A special endeavor was made to detect any possible correlations between the anxious coping processes and the degree of diabetic control.

The reported results concern mainly the GF group in relation to the P group.

1 Average age at diagnosis of diabetes was significantly higher in the GF group than in the P group. In the cases studied in this material, all the children who had developed diabetes prior to the age of three had poor control of their disease.

The duration of the illness in the GF group was significantly shorter than in the P group.

2 In the series diabetes was evenly distributed among males and females in both the GF group and the P group.

4 Studies of childhood diabetes have clearly demonstrated that diabetes is a recessive hereditary disease. 20 % of the juvenile diabetics having known diabetic relatives at the time of the diagnosis of their disease. In the series 37 of the 60 diabetic children (63 %) had relatives known to be diabetic at the time when the whole series had been collected.

The high percentage of diabetic relatives in the series can be explained, at least partly, by the facts that between the time of the first diagnosis and the last examination 1) new cases of diabetes manifested among the child's relatives and 2) cases of diabetes among more distant, perhaps already deceased relatives came to the parents' knowledge.

Ripstein and co-workers in their review of the available data concerning the hereditary transmission of diabetes come to the conclusion that the clinically prominent diabetes has reliable genetic ground and thus support the hypothesis of multifactorial heredity. According to their opinion

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Larsson and Sterky pointed out that, in their Swedish study of juvenile diabetics who had reached adulthood, in 12.9 per cent of men and 3.3 per cent of women the height was below the lower normal limit. No explanation was found for the tendency towards short stature of these patients. They did not deviate from the rest of the cases with regard to age at onset, duration, chronological age, food habits, blood sugar level, insulin requirements or extent of vascular damage. (88)

The presence of stunted growth at the time of last examination in this series is 13.3 % (3.3 % in the GF group and 23.3 % in the P group).

The figures are too small for statistical evaluation. Moreover they cannot be considered as final because the majority of the have not yet reached adult stature. A tendency is, however, for the heights to be below the lower normal limit more often in the P group than in the GF group.

Swift and co-workers found that the birth rank of the childhood diabetic was significantly associated with the diabetic control. In their sample in contrast to the present study the eldest child in the family had significantly worse control than did children of other birth rank. (132) According to the findings of this study

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the eldest child's diabetes is rarely poorly controlled. The discrepant findings of this study may be due to the limited sample or to other factors e.g. cultural ones.

7 In this study the social status of the family seems to be correlated with the diabetic control. The Social Groups I and II were more frequently found in the P group than in the GF group.

8 The incidence of mothers gainfully employed was small in each diabetic group when compared with the over all incidence of gainfully employed married women in Finland. The difference can be partly explained by the restrictions caused by the child's illness partly by the fact that our Children's Hospital serves a large number of country communities where — for many reasons — the mothers can not go to work away from the home as easily as the mothers in cities and industrial centers.

There were more mothers working away from home in the P group than in the GF group. The difference however is not statistically significant.

9 The assessment of the family situation and the parents' mental and psychosomatic health gave the following evaluation.

All the diabetic children in this series seem to come from relatively stable homes. This appraisal is based on relatively few contacts with the parents however.

The incidence of emotional disturbances and psychosomatic conditions in the parents was about the same in the two diabetic groups.

10 There are 2 children in the GF group and 6 in the P group who exhibited *neurotic or characterological symptoms* before the diagnosis of diabetes. The figures are too small for statistical evaluation. On the other hand these figures are only minimum ones because they include only those symptoms which the parents were aware about and worried at the time of the diagnosis of the child's diabetes. It is a general observation that the mental symptoms in young children often pass unnoticed by the parents or are attributed to the child's normal immaturity. This is especially true of the two-year-olds of which there were 7 in the P group.

11 According to the findings of this study the incidence of stressful situations was about the same in the two diabetic groups. In three cases, one belonging to the GF group and two to the P group either the mother or the child spontaneously connected the event with the onset of the child's diabetes.

Emotional stress is a widely discussed topic in both popular and scientific writing, often with no attempt to define what is meant.

In this paper the term "emotional stress" has the meaning given by Engel (40) and Stenbäck (130). Engel offers this definition: "Psychological stress refers to all processes whether originating in the external environment or within a person, which impose a demand or requirement upon the organism the resolution of which requires activity of the mental apparatus before any other system is involved or activated." Stenbäck uses the term "life stress" to describe all things in the life of the patient which the patient himself experiences as "stress" or which by sociological investigation are established as circumstances producing disturbances in human life. Both authors draw a distinction between the initiator or producer which Engel names "psychological stress" and Stenbäck "life stress" and the effects, which Engel calls "tension" and Stenbäck "internal experience of stress". In a child's life stress situations are usually those demanding independent action or implying separation from parents.

Goldner states that the roles of environmental influence and of stress are relatively easy to determine where the onset of the disease is sudden and readily recognizable and where the etiological mechanisms are known. In diabetes mellitus however we are dealing with a hereditary or genetic predisposition and moreover with a disease which usually has an inconspicuous and insidious onset. Stressful life situations on the other hand, are common. With some imagination one can find in each diabetic history coinciding with the first manifestation of the disease, an event which could be described as a causative stress. Critical analysis however will show that similar events occur just as frequently in the histories of healthy people and non-diabetic patients. Only careful case analysis of the specific aspects of an individual case, with proper consideration of the past history, the severity, the duration of the stress situation and its proximity to the manifestation of the diabetes, can reveal the probability of a causal relationship. (51)

With these reservations in mind, one quickly realizes that in a research project like the present a detailed analysis of each case cannot be made. The findings therefore only indicate a potential causality between the stress situation and the manifestation of diabetes mellitus.

12 The family's immediate reaction to the illness of their child was often characterized by feelings of bewilderment and shock, anxiety fears and depressive feelings, which were often accompanied by feelings of guilt. In some instances the child's illness apparently brought out the parents' aggressive feelings, which were then directed towards the child or the persons in charge of the child's treatment. In some instances the parents consoled themselves with wishful thinking, usually imagining that their child's illness was not a chronic one.

The differences in the parents' immediate reactions between the two diabetic groups were mainly in the presence of initial insomnia and wishful thinking, which were more common in mothers of the GF group than in those of the P group. There is a general trend, although statistically nonsignificant, for the mothers in the GF group to be more emotional, vivid and colorful in their immediate reactions.

13 Whenever diabetes is diagnosed in a child, the family has to adjust itself to the child's chronic illness and the limitations and alterations this brings into the day-to-day life of the family. At the same time, the members of the family have to learn how to handle their feelings of anxiety, depression, etc. Thus the adaptive processes take place at two different levels at the same time. In this study these two-level adaptive processes are called the *external* and *internal coping processes*. In terms of external coping it

was found that constructive coping devices were much more common in the GF group than in the P group. Accordingly non-constructive coping processes, mainly helplessness and poor co-operation in the daily care of the diabetic child, were more frequent findings in the P group.

The main areas where the family's coping with the child's illness can be observed are the diabetic diet and the insulin injections. It was found that constructive coping apparently was greatly promoted by good co-operation and sharing of responsibility among members of the family. Every one of those families in which other members of the family have adopted the child's diet belongs to the GF group. Correspondingly to the GF group there are significantly more families in which more than one member takes share in giving the daily insulin injection.

One of the main objectives of this study was to comprehend some of the parents' inner motivations, which could cause their external coping behavior.

Apparently all parents try to care for their diabetic child in the way which, in their judgement, is most beneficial for the child. It has been demonstrated elsewhere that difficulties in daily diabetic care are often the cause of lability and great shifts in the patient's metabolic state. (134)

In this study it was established that there was positive correlation between constructive external coping processes and constructive internal coping processes, which in this connection means ability to adequately work through and control the feelings of anxiety, loss and depression. In many instances the parents find some enjoyment in caring for their sick child, who because of his sickness, remains more closely attached to the parents.

Correspondingly the non-constructive external coping devices show positive correlation with the non-constructive internal coping, in these cases mainly denial, omnipotent thinking, depression and phobias.

14 The child's immediate reaction to the discovery of diabetes could only be evaluated in those cases in which the child's first hospitalization occurred at the time of the study or in cases where either the mother or the hospital record provided sufficient data. Additionally it would require more detailed case studies to be able to differentiate between the child's reaction to his illness and his reaction to the hospitalization. However from the findings of this study it seems probable that the severity of the child's first reaction does not relate to the later controllability of his diabetes. It may even be that child who in the first stage of his illness is able to give vent to his anxiety can better work it through and become able to handle it later on.

15 The child's later adjustment was considered in terms of

- a) the symptomatic reactions and
- b) the general evaluation of his adjustment at home at school and in hospital and/or out patient department visits.

The symptomatic reactions exhibited by the children percept the following remarks:

A. Disturbances Related to Bodily Functions: There are 5 children in the GF group and 8 children in the P group who at the age of 4 were still enuretic.

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- a) the symptomatic reactions and
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The symptomatic reactions exhibited by the children prompt the following remarks

A. Disturbances Related to Bodily Functions. There are 5 children in the GF group and 8 children in the P group who at the age of 4 were still enuretic.

Authors disagree about the exact age at which a child can be labeled as enuretic. In this study the figures reported by Bellman and Hallgren are used as comparative data (8-54). Both set the age limit for enuresis at 4 years.

Bellman found the incidence of enuresis at an average age of $7\frac{1}{4}$ years to be 5.8 %. In this study the number of children who were still enuretic at the age of 8 years was 7 (13 %).

Of the 13 children who were enuretic after the age of 4, 10 were boys and 3 girls. This is in accordance with other studies which indicate that enuresis is more frequent in boys than in girls.

Enuresis is generally regarded as a symptom with heterogeneous etiology. Where diabetes is concerned both somatic and psychogenic factors related to enuresis should be considered.

a) one of the more frequent symptoms of polyuria in diabetes is bedwetting.

b) enuresis sometimes develops after a physical illness, especially if the examination or treatment procedures have centered around the genitourinary system. In diabetes, urinalysis is part of the daily routine. Bedwetting might even in some cases be an unconscious way of escaping from the urinalysis if the child knows that he has eaten something forbidden.

c) in the literature enuresis is generally regarded as a sign of immaturity. It is also thought that enuretic children have difficulty in handling their aggressions.

In individual cases more than one of the above mentioned etiological factors may operate simultaneously.

Speech and language disturbances were found only among the children belonging to the P group.

II Developmental Difficulties

There was one case of excessive separation anxiety and one case of manifest problems in sexual identification both belonging to the P group.

C. Disturbances in Social Behavior

Aggressive, antisocial and oppositional behavior disturbances were found almost entirely in the P group. This is especially true of oppositional behavior (passive resistance, passive aggressive behavior, disobedience and running away) which appears only in the P group. Although the figures are too small for any far-reaching conclusions

antisocial and oppositional behavior can be singled out as behavior types specific to the P group.

D. Disturbances in Affective Behavior

In contrast to the oppositional behavior and manifestly fearful behavior were more frequent in the GF group than in the P group.

E. Difficulties in Integrative Behavior

Difficulties in integrative behavior were found in 3 cases of the GF group and in 7 cases of the P group.

In the general evaluation of the child's late adjustment it was discovered that normal adjustment and mild adjustment disorders were more frequent in the GF group than in the P group. Accordingly, psychoneurosis and personality trait disorders were more frequent in the P group.

16. A greater proportion of children in the GF group were at the top of the form. One fifth of the children in the P group had had to repeat a class in the elementary school, whereas this phenomenon had not occurred among the children in the GF group.

17. The intelligence test revealed no statistically significant difference between the children in the GF group and those in the P group. The distribution curves thus show good agreement with the average curve. The investigation thus suggests that:

a) intelligence is of no specific importance for diabetic control.

b) the better academic success of the children in the GF group is apparently caused by factors other than intelligence.

18. The Rosenzweig Picture Frustration Test, analyzing the child's attitudes to different frustrating situations, revealed no statistically significant differences between the two diabetic groups.

When the diabetic children were compared with normal control subjects the findings were as follows:

The only statistically significant difference between the normal group and the diabetic group was found in Reaction Types. In frustrating situations the children of the normal group were

more ego-defensive and more person-oriented than the diabetic children.

18 The Discrimination Analysis of the Holzman Likert Technique scores shows that the two diabetic groups differ clearly from each other on the Discriminant Line. There is only one exception, a child belonging clinically to the G group, whose Discrimination Points locate him in the middle of the P group.

For this series those best discriminative variables were Integration, Populist Movement, Animal, Color Shading, Barrier and Hostility. The major dimensions measured by these variables are as follows.

Holzman Factor I Perceptual Maturity and Integrated Ideational Activity A high amount of this factor would be indicative of well organized, ideational activity good imaginative capacity well differentiated ego boundaries, and awareness of conventional concepts.

Holzman Factor II Perceptual Sensitivity

This factor involves sensitivity to the stimulus qualities of the blood. Reactions to Color and Shading are indicators of affective responsiveness and rich fantasy life.

According to the HIT results the children in the GF group have more integrated, more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts. In addition, the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group.

This study has disclosed number of variables related to the control of childhood diabetes in this series. The findings of this study do not necessarily mean that the variables disclosed are independent ones. For example the age at the diagnosis was found to be significantly correlated with the control of diabetes, being earlier in the P group. At the same time, the mother omnipotent thinking concerning the child illness was found to be correlated with Poor Control of diabetes. But it is possible that the great dependency of young child upon the mother is apt to evoke in the mother the feeling that the child illness belongs entirely to her.

Accordingly if the child is older at the diagnosis of diabetes, he has already had a chance to establish himself as a separate individual with responsibility for his own body and illness. It can be argued that this phenomenon is also apparent in the HIT results, where the children in the GF group give responses indicating significantly better integrated ego-boundaries.

In the light of these results it might be useful to re-examine the techniques that have been developed to meet the emotional needs of families of diabetic children. The first step in many cases might be the confrontation and reduction of the child's anxiety and also the parents'. In the light of this study it seems that when the mother's anxiety and depression had not been adequately dealt with at the start, they tended to affect her ability to cope with the child's illness.

Educative efforts are provided by all clinics treating diabetic children. The aim is to teach the parents and children about diabetes. But these efforts should be geared so that the anxiety and depression are at least somewhat relieved before the education is offered.

In the light of this study it seems important to stress the value of the co-operation of all members of the family in the care of the child's diabetes. Understandably it is hard to teach the child self-care of insulin injections if one or more members of the family morbidly fear the injections. Swift and co-workers have concluded that too often the fact that the child with diabetes is different is denied, and the child has been assured that he is *no different* (135). These impressions are in agreement with the findings of this study where massive denial of the child's illness was found to be positively correlated with Poor Control of the child's diabetes. A confrontation aimed at securing the honest admission that the child has chronic disease which makes him different from his healthy age-mates, combined with highlighting the intact areas of functioning, seem to aid the family in achieving the best overall adjustment and at the same time better control of the child's diabetes.

Authors disagree about the exact age at which a child can be labeled as enuretic. In this study the figures reported by Bellman and Hallgren are used as comparative data (8-54). Both set the age limit for enuresis at 4 years.

Pellman found the incidence of enuresis at an average age of $7\frac{1}{4}$ years to be 58.96%. In this study the number of children who were still enuretic at the age of 8 years was 7 (13.96%).

Of the 13 children who were enuretic after the age of 4-10 were boys and 3 girls. This is in accordance with other studies which indicate that enuresis is more frequent in boys than in girls.

Enuresis is generally regarded as a symptom with heterogeneous etiology. Where diabetes is concerned, both somatic and psychogenic factors related to enuresis should be considered.

a) one of the more frequent symptoms of polyuria in diabetes is bedwetting.

b) enuresis sometimes develops after a physical illness, especially if the examination or treatment procedures have centered around the genitourinary system. In diabetes urinalysis is part of the daily routine. Bedwetting might even in some cases be an unconscious way of escaping from the urinalysis if the child knows that he has eaten something forbidden.

c) in the literature enuresis is generally regarded as a sign of immaturity. It is also thought that enuretic children have difficulty in handling their aggressions.

In individual cases more than one of the above mentioned etiological factors may operate simultaneously.

Speech and language disturbances were found only among the children belonging to the P group.

B. Developmental Difficulties

There was one case of excessive separation anxiety and one case of manifest problems in sexual identification both belonging to the P group.

C. Disturbances in Social Behavior

Aggressive, antisocial and oppositional behavior disturbances were found almost entirely in the P group. This is especially true of oppositional behavior (passive resistance, passive-aggressive behavior, disobedience and running away) which appears only in the P group. Although the figures are too small for any far-reaching conclusions

antisocial and oppositional behavior can be singled out as behavior types specific to the P group.

D. Disturbances in Affective Behavior

In contrast to the oppositional behavior, anxious behavior and manifestly fearful behavior were more frequent in the GF group than in the P group.

E. Difficulties in Integrative Behavior

Difficulties in integrative behavior were found in 3 cases of the GF group and in 7 cases of the P group.

In the general evaluation of the child's later adjustment it was discovered that normal adjustment and mild adjustment disorders were more frequent in the GF group than in the P group. Accordingly, psychoneurosis and personality trait disorders were more frequent in the P group.

16. A greater proportion of children in the GF group were at the top of the form. One fifth of the children in the P group had had to repeat a class in the elementary school, whereas this phenomenon had not occurred among the children in the GF group.

17. The intelligence test revealed no statistically significant difference between the children in the GF group and those in the P group. The distribution curves thus show good agreement with the average curve. The investigation thus suggests that:

a) intelligence is of no specific importance for diabetic control.

b) the better academic success of the children in the GF group is apparently caused by factors other than intelligence.

18. The Rosenzweig Picture Frustration Test, analyzing the child's attitudes to different frustrating situations, revealed no statistically significant differences between the two diabetic groups.

When the diabetic children were compared with normal control subjects, the findings were as follows:

The only statistically significant difference between the normal group and the diabetic group was found in Reaction Types in frustrating situations: the children of the normal group were

more ego-defensive and more person-oriented than the diabetic children.

13 The discrimination analysis of the Holzman Labeling Technique scores shows that the two diabetic groups differ clearly from each other on the Discriminant Loe. There is only one exception, child belonging clinically to the GF group, whose Discrimination Points locate him in the middle of the P group.

For this series those best discriminative variables were Integration, Popular Movement, Arousal, Color Shading, Barrier and Hostility. The major dimensions measured by these variables are as follows:

Holzman Factor I Perceptual Maturity and Integrated Ideational Activity. A high amount of this factor would be indicative of well organized, ideational activity, good imaginative capacity, well differentiated ego boundaries, and awareness of conventional concepts.

Holzman Factor II Perceptual Sensitivity. This factor involves sensitivity to the stimulus qualities of the blobs. Reactions to Color and Shading are indicators of affective responsiveness and rich fantasy life.

According to the HIT results the children in the GF group have more integrated, more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts. In addition the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group.

This study has disclosed a number of variables related to the control of childhood diabetes in this series. The findings of this study do not necessarily mean that the variables disclosed are independent ones. For example the age at the diagnosis was found to be significantly correlated with the control of diabetes, being either in the P group. At the same time the mother omnipotent thinking concerning the child's illness was found to be correlated with Poor Control of diabetes. But it is possible that the great dependency of young child upon the mother is apt to evoke in the mother the feeling that the child's illness belongs entirely to her.

Accordingly if the child is older at the diagnosis of diabetes, he has already had chance to establish himself as a separate individual with a responsibility for his own body and illness. It can be argued that this phenomenon is also apparent in the HIT results where the children in the GF group give responses indicating significantly better integrated ego-boundaries.

In the light of these results it might be useful to re-examine the techniques that have been developed to meet the emotional needs of families of diabetic children. The first step in many cases might be the confrontation and reduction of the child's anxiety and also the parents. In the light of this study it seems that when the mother anxiety and depression had not been adequately dealt with at the start they tended to affect her ability to cope with the child's illness.

Educative efforts are provided by all clinics treating diabetic children. The aim is to teach the parents and children about diabetes. But these efforts should be geared so that the anxiety and depression are at least somewhat relieved before the education is offered.

In the light of this study it seems important to stress the value of the co-operation of all members of the family in the care of the child's diabetes. Understandably it is hard to teach the child self-care of insulin injections if one or more members of the family morbidly fear the injections. Swift and co-workers have concluded that too often the fact that the child with diabetes is different is denied, and the child has been assured that he is no different. (135) These impressions are in agreement with the findings of this study where massive denial of the child's illness was found to be positively correlated with Poor Control of the child's diabetes. A confrontation aimed at securing the honest admission that the child has a chronic disease which makes him different from his healthy age mates, combined with highlighting the intact areas of functioning, seems to aid the family in achieving the best overall adjustment and at the same time better control of the child's diabetes.

Summary

The aim of the present study was to search for both the immediate reactions to the diabetes and the more permanent coping processes in diabetic children and their parents. A special attempt was made to detect possible correlations between the various external and internal coping processes and the adequacy with which the diabetes was controlled.

In addition to the above-mentioned aim of the study the investigation was concerned with a number of factors affecting diabetic control both medical social and socio-psychiatric. The investigation was conducted on 60 diabetic children and their parents. Of these 60 children 30 had Good or Fair Control (GF) and 30 had Poor Control (P) of the diabetes. The criteria of diabetic control were in terms of growth acetonuria, 24-hour quantitative urine glucose fasting blood sugar and number of hospitalizations per year.

The investigation involved interviews and play observations with the children and interviews with the parents. One interview with each parent was a structured one, in which a special questionnaire was gone through.

Estimates of the children's scholastic achievements, adjustment to school and teachers and relations with peers were obtained from their teachers.

The psychological examination of each child comprised an intelligence test of Stanford-Binet type (Terman-Merrill Lehtovaara) and two personality tests (Rosenzweig Picture Frustration Test and Holzman Inkblot Technique).

Medical data on the children were collected from their hospital and outpatient records. Those children who were hospitalized during the time of collecting the series (September 1964 — December 1967) were observed on the ward and in group situations. At the same time observations were made on parent-child interactions during visiting hours.

The family's immediate reaction to the illness of their child was often characterized by feelings of bewilderment and shock, anxiety fears and depressive feelings. Initial insomnia and wishful thinking were more common in mothers of the

GF group than in those of the P group. There is a general trend, although non-significant statistically for the mothers in the GF group to be more emotional and vivid in their immediate reactions.

The external coping processes were more constructive in the GF group than in the P group. On the other hand non-constructive coping processes mainly helplessness and poor co-operation in the daily care of the diabetic child were frequent findings in the P group.

It was found that constructive coping apparently was greatly promoted by good co-operation between all members of the family and shared responsibility for seeing that the child followed the correct regimen.

The constructive internal coping processes which in this connection means the ability to adequately work through and control the feelings of anxiety loss and depression were found to be positively correlated with constructive external coping processes. On the other hand, the way in which the P group families inwardly coped with the anxiety and depression showed more pathological and extreme forms mainly denial, omnipotent thinking chronic underlying depression and phobias.

The child's immediate reaction to the discovery of diabetes could not be evaluated in all cases. The findings of this study do not suggest that the severity of the child's first reaction determines the later controllability of his diabetes.

The children in the GF group had fewer and less pathological symptomatic reactions and better later adjustment than the children in the P group. The P group was found to be more extreme and/or pathological in the number of symptomatic reactions as well as in the psychiatric clinical ratings.

The GF group showed better academic achievement than the P group.

Statistical analyses showed no differences between the two diabetic groups in terms of hereditary predisposition to diabetes family size, IQ of the children or the results in the Rosenzweig Picture Frustration Test.

Statistical differences were found in the age at first diagnosis of diabetes and in the duration of the illness. In addition, the two groups were significantly or almost significantly alike in social class of the family and birth rank of the diabetic child. On independently scored Holzmann I klot Technique data, the GF group showed

better organized ideational capacity better differentiated ego-boundaries and more imaginative and sensitive personalities. On the other hand, the P group showed less integrated, less imaginative and less sensitive personalities with more pathological ego boundaries and stronger aggressiveness.

Acknowledgements

I am indebted to the late Professor Toivo Salmi M.D. Children's Hospital University of Turku who started the child psychiatric services in the Clinic headed by him and followed the early phase of my work with keen interest.

Professor Tuomas Peltonen, M.D. Head of the Children's Hospital University of Turku has unfailingly encouraged and stimulated my work with interest and objectivity. It is hard to find words to express my gratitude to him.

Professor Asger Stenback M.D. in the preparatory phase of this study supplied me with valuable advice based on his thorough knowledge of psychiatric research. My best thanks are due to him.

My thanks are also due to Dr. Elsa Brita Nordlund child psychiatrist Karolinska Sjukhuset Stockholm who read my typescript and gave me valuable comments and advice based on her knowledge and experience in the field of child psychiatry.

Mr. Pentti Sinisalo and Mr. Tapio Korhonen Mag. Phil. performed the psychological examinations of the children. I am grateful for their valuable co-operation.

I am grateful to Mr. Pekka Lehtio Mag. Phil. who made the statistical analyses and programmed the data processing.

Mrs. Aili Ryyänen M.A. and her assistants at the Library of the Medical Faculty University

of Turku helped me in collecting the literature. My sincere thanks are due to them.

Mrs. Inkeri Perälä the occupational therapist, who observed the children in group situations, has contributed greatly to the data.

Mrs. Jean Margaret Perttunen B.Sc. and Mr. Sidney D. Berger have revised the language of the manuscript. In addition to this they have given me valuable advice and support for which I am deeply grateful to them.

I wish to express my gratitude to the personnel of the Children's Hospital for their assistance during the study.

My sincere thanks are also due to the families who participated in this study.

The investigation was supported by grants from the Foundation for Pediatric Research in Finland from the Yrjö Jahnsson Foundation and from the Psychiatric Association in Finland.

Here I wish to acknowledge their valuable support.

Last but not least I wish to thank my 4 sons who have shared the burden of the work with me and who have taught me much about coping in stressful life situations.

Loppu August 1969

Majja-Liisa Koski

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Appendixes

Structured interview with the parent

A The parent's immediate reaction to the illness of the child.

- 1 Could you tell me what kind of feelings or thoughts you had when you first got to know that your child had diabetes?
- 2 Did you cry? For how long?
- 3 Could you sleep? How many sleepless/almost sleepless nights did you have?
- 4 For how long did those first feelings and thoughts last? As time went on, did they change? If they changed, what kind of feelings and thoughts have on now about your child's illness?

B The coping processes

- 1 Now when your son/daughter has been sick for _____ years, what do you now think about his/her illness?
- 2 The diet and the insulin injections are both part of the daily care of the diabetic. Which one is more difficult for you?
- 3 Could you describe your son's/daughter's morning schedule? What do you speak about in the mornings?
- 4 How does your son/daughter react to the diet?
How does his/her diet differ from that of the other members of the family?
How often does your child ask for sweets?
How often do you indulge him?
- 5 How does your son/daughter react to the insulin injections? Who gives the injections? Does your child ever do it himself?
- 6 How long did it take before you became skilled in giving the injections?
- 7 How long did it take before you got used to our child diet?
- 8 What do you do if the urinalysis reveals acids in your child urine?
- 9 Do you speak about your child illness to home? What do you say about it? How often? Do you speak about it with friends and relatives?

- 10 Do your child's friends know about his/her diabetes? How do they react to it?
- 11 Do your child's teachers know about his/her diabetes? Who informed them? In what way? How did they react to it?

C The child

- 1 Has your child changed during his/her illness? In what way?
- 2 Could you tell me what kind of child he/she was before the diabetes? What kind of a child is he/she now?
- 3 Does your son/daughter look sad, depressed or unhappy most of the time/sometimes/never?
- 4 Is he/she interested in things or does he/she look bored or uninterested often? How often does he/she tell you interestingly what he/she has seen or done?
- 5 Is he/she able to enjoy his/her life?
- 6 How does he/she react to frustrations?
- 7 How is his/her sleep?

2 Q u e s t i o n n a i r e t o t h e t e a c h e r

- 1 I _____ level of child name achievement higher/the same/lower than the average level of his/her class?
- 2 Are his/her achievements more even/the same/more changing than the average of the class?
- 3 What are his/her best subjects?
- 4 What are his/her weakest subjects?
- 5 Compared with his/her classmates, is he/she interested in things/bored and uninterested?
- 6 What things interest him/her?
- 7 Does he/she seem to take the school positively/indifferently/negatively?
- 8 How does he/she react to frustrations?
- 9 How is his/her relationship with the teachers?
- 10 How is his/her relationship with peers?
- 11 Could you tell me anything else which could have meaning when his/her scholastic achievement is evaluated.

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Appendixes

5. Structured interview with the parent

A. The parent's immediate reaction to the illness of the child

- 1 Could you tell me what kind of feelings or thoughts you had when you first got to know that your child had diabetes?
- 2 Did you cry? For how long?
- 3 Could you sleep? How many sleepless/almost sleepless nights did you have?
- 4 For how long did those first feelings and thoughts last? As time went on, did they change? If they changed, what kind of feelings and thoughts had you now about your child's illness?

B. The coping processes

- 1 How long your son/daughter has been sick for _____ years what do you now think about his/her illness?
- 2 The diet and the insulin injections are both part of the daily care of the diabetic. Which one is more difficult for you?
- 3 Could you describe your son/daughter's morning schedule? What do you speak about in the mornings?
- 4 How does your son/daughter react to the diet?
How does his/her diet differ from that of the other members of the family?
How often does your child ask for sweets?
How often do you indulge him?
- 5 How does your son/daughter react to the insulin injections? Who gives the injections? Does your child ever do it himself?
- 6 How long did it take before you became skilled in giving the injections?
How long did it take before you got used to your child's diet?
- 7 What do you do if the urinalysis reveals acids in our child's urine?
- 8 Do you speak about your child's illness at home? What do you say about it? How often? Do you speak about it with friends and relatives?

- III Do your child's friends know about his/her diabetes? How do they react to it?
- 11 Do your child's teachers know about his/her diabetes? Who informed them? In what way? How did they react to it?

C. The child

- 1 Has your child changed during his/her illness? In what way?
- 2 Could you tell me what kind of child he/she was before the diabetes? What kind of a child is he/she now?
- 3 Does your son/daughter look sad, depressed or unhappy most of the time/sometimes/never?
- 4 Is he/she interested in things or does he/she look bored or uninterested often? How often does he/she tell you interestingly what he/she has seen or done?
- 5 Is he/she able to enjoy his/her life?
- 6 How does he/she react to frustrations?
- 7 How is his/her sleep?

2. Questionary to the teacher

- 1 Is _____ a level of child's name achievement higher/the same/lower than the average level of his/her class?
- 2 Are his/her achievements more even/the same/more changing than the average of the class?
- 3 What are his/her best subjects?
- 4 What are his/her weakest subjects?
- 5 Compared with his/her classmates, is he/she interested in things/bored and uninterested?
6. What things interest him/her?
- 7 Does he/she seem to take the school positively/indifferently/negatively?
8. How does he/she react to frustrations?
- 9 How is his/her relationship with the teachers?
- 10 How is his/her relationship with peers?
- 11 Could you tell me anything else which could have meaning when his/her scholastic achievement is evaluated.

Some drawings of the diabetic children



Figure 6 Drawing of a boy 13 yrs belonging to the P group This drawing was made on the ward and makes an artificially gay impression



Figure 8 Drawing of a girl 9 yrs belonging to the P group The Christmas tree was placed far in the left hand corner of the paper There are decorations only on one side of the tree

Figure 7 Drawing of the same boy as Fig 6 Made on the same day during a psychiatric interview It makes an unhappy and empty expression



Figure 9 Drawing of a boy 11 yrs belonging to the P group An injection is given to a patient

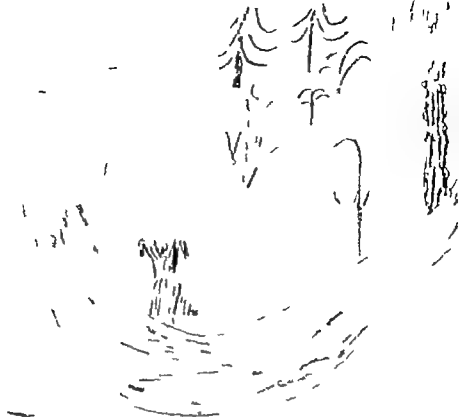


Figure 10. Drawing of a girl 9 yrs belonging to the GP group Both the female figures are well drawn The unproportionally tall girl in the centre was stated by her to be dwarf girl She has big, sad eyes and short arms The story told by the girl is as follows On the other side of the forest there is the house of a witch The witch is looking through her window A dwarf girl stands in her own yard beautifully dressed There is path from the witch's house to the dwarf house along that path the witch sneaks in the nights

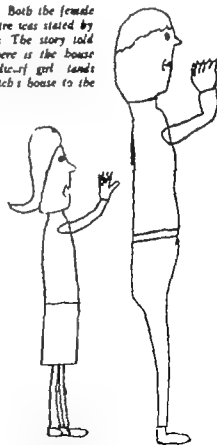


Figure 11 Drawing of boy 11 yrs belonging to the P group Both the male figure (left) and the female figure (right) are drawn in profile They make somewhat empty and lonely expression Y is the stories told by the boy indicates at least a desire for a companion too

The male fig. This is like a boy saying hello to his friend

The female figure "The looks more like a not blinking girl"

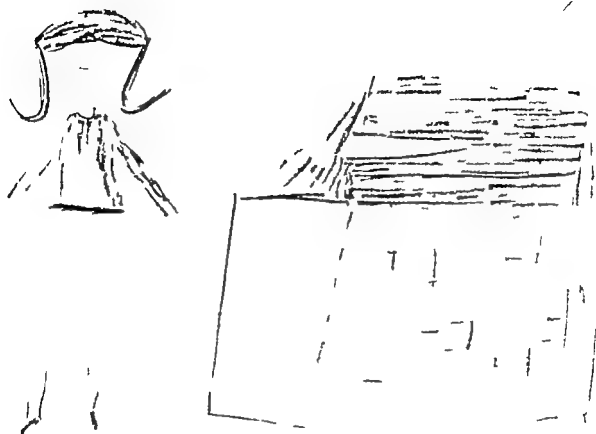


Figure 12 Drawing of a girl 6 yrs belonging to the GF group Better than average drawing skill
The most striking feature is the tallness of the girl compared with the house

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PSEUDOMONAS INFECTIONS IN
A PAEDIATRIC SURGICAL UNIT

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Acknowledgements

The subject of the present investigation was suggested to me by Professor Nillo Hallman, M.D. and his excellent advice and never failing interest in my work were a most encouraging support to me.

Dr. Paa = Makela, M.D. has from the very beginning of my work given me all kinds of help, advice and friendly criticism. Professor Ilari Rantatalo, M.D. and Professor Ossi Pettay M.D. have spent time in reading the manuscript and they have given me valuable advice and criticism.

Professor Lars Hjelt, M.D. has kindly given me the results of cytological and histological examinations. Dr. Juhani Rapola, M.D. examined the specimens for specific histological changes.

Mrs. Irja Kohonen, B.N. was a skillful and experienced assistant in the laboratory work. The mathematical analysis was carried out by Mr. Sampo Salonsara, Techn. D. Mr. E. Linkeola drew the illustrations and Miss Elvi Kanbokallio translated the manuscript into English with great skill and experience.

I wish to express my warm thanks to them all.

I am also very grateful to the staff of the Children's Hospital of the University of Helsinki for pleasant co-operation and assistance during the study.

The study was financially aided by the Foundation for Paediatric Research in Finland.

Rovaniemi, January 1969

Riitta Sorila

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Introduction

Over two decades ago there was observed an increasing occurrence of outbreaks of hospital infection due to *Staphylococcus aureus*. At the same time an increase was seen in infectious diseases caused by gram-negative bacilli (7, 53, 73, 150, 180). This increase probably occurred to a marked degree on the basis of hospital infection, in the etiology of which the gram-negative bacilli have in recent years attained equal significance with the staphylococcus or even have replaced it as the chief causative agent (7, 23, 60, 84, 132, 160).

Among these gram-negative bacilli the most notorious cause of hospital infection is *Pseudomonas aeruginosa*. Previously it very rarely was

the causative agent, but during approximately the past 20 years a very large number of studies have been published on infections and hospital epidemics due to *Pseudomonas* (10, 15, 53-55, 56, 61, 72, 84, 118, 160, 161, 180).

Cases of infection ascribable to gram-negative bacilli, particularly to *Pseudomonas*, were observed to have increased in the Children's Hospital of the Helsinki University Central Hospital, especially in its surgical unit for children under 2 years of age and in the newborn ward (132). For this reason there was considered to be reason to undertake a study for clarification of the characteristics and significance of these *Pseudomonas* infections.

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Cases of infection ascribable to gram-negative bacilli, particularly to *Pseudomonas*, were observed to have increased in the Children's Hospital of the Helsinki University Central Hospital especially in its surgical unit for children under 9 years of age and in the newborn ward (152). For this reason there was considered to be reason to undertake a study for clarification of the characteristics and significance of these *Pseudomonas* infections.

Review of the Literature

Bacteriological Properties of *Pseudomonas aeruginosa*

Pseudomonas is a large genus of bacteria containing numerous water and soil organisms present everywhere in nature and usually apathogenic to man. The only species actually pathogenic to humans is *Pseudomonas aeruginosa* which also occurs in nature in various humid environments, especially in sewage water (30, 90, 177).

Pseudomonas aeruginosa is a gram negative motile rod shaped bacterium. It grows aerobically in all nutrient media readily forming the typical colony. The *Pseudomonas* may produce haemolysins as well as a green pigment of two types: the blue-green pyocyanine and the yellow-green fluorescein. It can usually be differentiated readily from other gram negative bacilli by biochemical reactions. The optimum temperature for the *Pseudomonas* is +37° C, but it can multiply at temperatures between +5° and +12° and is destroyed at +55° within 1 hour (177). An apathogenic member of the genus, *Pseudomonas fluorescens*, also produces fluorescein but does not grow at +42° or form pyocyanine (30, 177).

The *Pseudomonas* produces an endotoxin which, like those of other gram negative bacilli, is a lipopolysaccharide and which on injection into experimental animals gives rise to symptoms of shock (177, 177).

Serologically a number of types are recognizable on basis of both their flagellar and somatic antigens (50, 54, 99, 177) as well as by means of pyocine, the bacteriocine produced by the bacterium (41). Groups possessing similar lytic properties can also be distinguished by means of bacteriophages (50, 177).

Occurrence of *Pseudomonas aeruginosa* in Man

In the normal bacterial flora of the human skin and mucous membranes the *Pseudomonas* is conspicuously rare except in hospital populations. Numerous publications report only 1 to 3 % of the examined persons to be faecal carriers of the organism (17, 18, 18, 90, 93, 94, 95), and its occurrence in the nose, throat or skin is evidently still more infrequent (99).

In hospital environments, and especially during hospital epidemics, carriers of *Pseudomonas* have been found in considerably larger numbers (14, 90, 93, 99, 114). In some investigations up to half of the patients have been carriers (116).

Likewise the *Pseudomonas* does not belong to the first bacterial flora of the skin and mucous membranes of the newborn infant (37, 57, 142, 119, 163, 173, 174). The reason probably is the rare occurrence of this organism in parturient vagina or faeces, the flora in which evidently forms the basis of a large part of the bacterial flora of the newborn (13, 35, 119, 173).

In the studies published from maternity hospitals and newborn nurseries there is considerable variation in the incidence of infants colonized with *Pseudomonas*, apparently depending on the epidemic situation at the various times (19, 92, 116).

Factors Favouring *Pseudomonas* Colonization

The high incidence of *Pseudomonas* carriers in various hospital series speaks for the probability that some special circumstances in the

hospital environment are favorable to *Pseudomonas* colonization. Factors that promote spread of the organism are probably the massiveness of the infection disseminated by the grossly infected patient (97, 99, 164, 167), the use of anous items of equipment that are difficult to clean, such as anasthesia apparatuses (71, 152, 161), respirators (125), oxygen equipment (45) and nebulizers (45, 110, 111, 112, 146), the abundant moisture used in the care of newborn infants (69), and the poor action against *Pseudomonas* of the commonly used disinfectants (12, 95, 98, 100, 120, 127).

Colonization-promoting factors may also be present in the hospital patients themselves. Generally it is difficult for a bacterium to gain foothold on skin or mucous membranes that already have a bacterial flora (155, 147, 177). This flora is lacking in the newborn, who usually acquires it during the first 1 to 3 days of life (44, 142, 163). On the other hand, the cutaneous and mucosal bacterial flora, usually of saprophytic nature sensitive to antibiotics, can be destroyed or at least reduced in number by the use of antibiotics, thus providing resistant bacteria good opportunity for colonization. It has been observed, in fact, that during antibiotic therapy the pharyngeal flora readily changes in about 5-7 days to one consisting mainly of gram-negative bacilli (52, 63, 105, 180).

The bacterial flora on the skin and mucous membranes of severely ill patients has also been found to be converted to a flora of gram-negative bacilli within a very short time, presumably also without the action of antibiotics (154).

Factors Influencing Development of *Pseudomonas* Infection

The pathogenicity of *Pseudomonas* to man is in general low and onset of infection even in colonized person therefore requires the presence of some factor that impairs the defence mechanism of the body. This may be rare individual weakness of antibody action ("U, 151), but

there also has been encountered among hospital patients certain groups that are especially susceptible to infections produced by *Pseudomonas*.

Newborn infants, premature in particular have been observed to be sensitive to all infections by gram-negative bacilli (8, 15, 46, 60, 72, 75, 118, 121, 150, 155). For the greater part this may be due to a clearly evident deficiency of immunoglobulins in premature and other newborn (8, 68, 144). Antibodies to gram-negative bacilli are present mainly in the gamma-M fraction of immunoglobulins, which does not pass from mother to child but which the newborn rapidly begins to form already during the first week of life (5, 144), probably in response to growth of intestinal bacillary flora of maternal origin (8, 144). Possibly the child is partly protected against these maternal bacilli by antibodies received both in gamma-G-globulin via the placenta and in breastmilk (8, 82).

Other properties of the newborn infant may also increase its sensitivity to infection. The thin skin, short trachea and open umbilical blood vessels offer infecting organisms ready access into the body (96). In premature babies the capacity of leucocytes to phagocytize *Pseudomonas* bacilli has been found to be definitely poorer than in the full-term newborn (35).

The frequently observed susceptibility of infants and also of older children to *Pseudomonas* infections (56, 40, 59, 72, 75, 81, 94, 155) is doubtless likewise based on antibody deficiency. It has been demonstrated that the content in serum of haemagglutinating antibodies to *Pseudomonas* is quite low up to the third year of life and that more marked rise is seen only in the sixth year of life (81).

Patients with burn wounds have appeared to be especially sensitive to *Pseudomonas* infections (81, 99, 167). The protein-rich exudate from the burnt area seems to form a good nutrient bed for infection, and in the absence of the normal protective barrier of healthy skin the infection can penetrate into the deeper tissues (162, 177). Furthermore, the antibody level of the patient with burns is depressed, presumably because of loss of protein through the lesion (81).

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In hospital environments, and especially during hospital epidemics, carriers of *Pseudomonas* have been found in considerably larger numbers (11 90 93 99 118). In some investigations up to half of the patients have been carriers (116)

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Factors Favouring *Pseudomonas* Colonization

The high incidence of *Pseudomonas* carriers in our hospital series speaks for the probability that some special circumstances in the

100 / (50 55, 77 155, 172). Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at about 80 / when endotoxin shock was present, and at 20 / in other cases (172).

Histologically the typical change in *Pseudomonas* infections is a diffuse acute vasculitis, with abundant bacteria on the vascular walls, and haemorrhages, thromboses and necroses in the adjacent tissues (55).

Epidemics Caused by *Pseudomonas*

In the non-hospital population the *Pseudomonas* is rarely the causative agent in primary infectious processes (55, 77 87 102, 129 177), and epidemics are also of rare occurrence except in hospitals. However there are reports of diarrhoea epidemics due to infected milk or well-water (17 143).

In hospitals, on the other hand, *Pseudomonas* has been the cause of epidemics, some of which have been quite large, and these hospital infections have increased considerably within the last two decades (19 50, 56, 55 55). They have been quite numerous in newborn and premature nurseries (10 21 22, 59 47 69 72, 89, 92, 94 113, 116 129, 152, 165, 167 178) and in urological and burns units (50, 81 99 106, 108, 109, 114 150, 167). They have also been reported from other units (17 18, 43, 127 158, 159, 167 176).

For the onset of hospital infection with *Pseudomonas* there are certain preconditions, which were brought out by Wahba in his investigation in 1955 (167). Using a combined pyocine and serological typing method he studied the *Pseudomonas* strains in different kinds of hospital wards. Where the incidence of infection was low the isolated strains were often of various types presumably brought in by patients and the infections were to a great extent otogenous. This situation he found in the eye, ear and surgical wards, whereas in the urological, burns and paediatric units certain strain often was dominant for some length of time and an

epidemic of clearly this type prevailed in the ward.

An essential factor in the onset of an epidemic appeared to be the number of infection-susceptible patients in the ward. When they were few in number the *Pseudomonas* spread slowly and the various cases were caused by different types of the micro-organism. When there were many patients of this kind, some given strains became predominant and was the cause of numerous cases of infection in the course of weeks or months.

Wahba summarized the situation by stating that whenever highly susceptible patients came in contact with heavy disseminators of the organism, cross-infection was common (167).

Routes of Transmission of *Pseudomonas* Infection

It is apparent that the *Pseudomonas* bacterium can spread in various ways, as by contact, by air or by way of contaminated hospital equipment (55, 60 175). The relative importance and share of these routes in the spread of the infection probably differ according to the hospital conditions and the type of patients.

Transmission by hands. A patient with burns, diarrhoea or urinary tract infection who is infected with *Pseudomonas* readily contaminates the hands of the nursing staff (54 99, 106). Often the bedding and urine bottles of these patients are also highly contaminated (54 99, 106 150) and handling them may probably also contaminate the hands.

Gram negative bacilli do not belong in the normal permanent bacterial flora of the skin and they disappear spontaneously (156, 177). However even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massive contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100). Since *Pseudomonas* is able to survive and even to grow

Cases of urinary tract infection with *Pseudomonas* have been described in patients with in dwelling catheter and in operated patients (55 100 108 130) Animal experiments have shown that obstruction or foreign bodies in the urinary tract predispose to infection even in the presence of a fully normal antibody level of the body (141)

The susceptibility to bacillary infections often seen in patients with leucæmia and aplastic anaemia and persons receiving radiotherapy or x ray treatment (15 19 25 56 75 166, 167 176) is held to be largely a result of lowering of the general resistance of cells and depression of antibody formation by irradiation as well as by antimetabolites and cortisone (24 67 115 177)

Patients with chronic pulmonary processes and fibrosis of the pancreas have been observed to be sensitive to *Pseudomonas* infection (42, 72 167 176) The basic disease in these cases probably lowers the resistance of the bronchial mucosa, rendering it easier for possible pathogenic pharyngeal bacteria to attack the bronchi (20 62, 86 91)

It is a generally accepted opinion that antibiotic therapy predisposes to *Pseudomonas* infections (15 175 180) The basis may be that colonization is facilitated by disappearance of the sensitive normal mucosal flora and that, at least in the newborn, antibody formation is weaker owing to disappearance of the innocent intestinal flora of maternal origin (8, 144 177) Experiments in vitro have also indicated that growth of some *Pseudomonas* strains is stimulated by tetracyclines or chloramphenicol (145)

Infections Due to *Pseudomonas*

The *Pseudomonas* may produce both localized infections foci as well as systemic infection. The incubation time is 5-7 days (116 155) When the infectious agent directly attacks the meninges (77) or the trachea (125 159) incubation requires only 1-2 days.

Infections of the external auditory canal and the middle ear are typical *Pseudomonas* infec

tions (55 123 165) However it is rarely encountered as the causative agent in acute otitis media, being more common in chronic processes in the ear (30 55 87 122, 155) It can cause infections of the eye of various kinds, from conjunctivitis to panophthalmitis (18, 30, 55) Burns and operation wounds may become infected (15 30 55 99 177) and likewise the umbilical stump of the newborn infant (92, 143, 155) Associated with *Pseudomonas* infections there are a great variety of skin symptoms, being evidently secondary signs of the septicæmia, and manifesting either as metastatic foci or toxic reactions (55)

The *Pseudomonas* has been found to give rise to respiratory tract infections of various kinds and degrees. Cases have been described of purulent rhinitis (115 155) bronchitis, pneumonia, abscess of the lungs and empyema (55, 143, 155) It has been found to cause localized infectious foci on the pharyngeal mucosa and in the parotid glands (59 55) as well as infections of the lower alimentary tract, diarrhoea of varying degree, and peritonitis (30, 54 55 94 143, 155) It has also been responsible for urinary tract infections (30 55 177) and meningitis (30 55 77)

All of the above conditions may lead to septicaemia, to which the newborn infant in particular is susceptible (55 56 118 143) Septicaemia has been found to develop especially on the base of infected operation wounds, burns, urological operations and umbilical infection (55 81 143, 172) but it can also occur without a clearly evident primary focus (55) Septicaemia due to *Pseudomonas* like bacteraemia from other gram negative bacilli may be accompanied by endotoxin shock (172)

In the published series of *Pseudomonas* infections the recovery and mortality incidences have varied over a wide range. They have doubtlessly been influenced by marked differences in the susceptibility to infection of the various patient groups as well as by fairly great differences in treatment. However mortality is almost without exception high in the more severe forms of disease, such as peritonitis meningitis and septicaemia with incidences ranging from 20 to nearly

100 % (40, 55, 77 155, 179). Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at about 80 % when endotoxin shock was present, and 120 % in other cases (172).

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It is apparent that the *Pseudomonas* bacterium can spread in various ways, as by contact, by air or by way of contaminated hospital equipment (35 60, 175). The relative importance and share of these routes in the spread of the infection probably differ according to the hospital conditions and the type of patients.

Transmission by hands. A patient with burns, diarrhoea or urinary tract infection who is infected with *Pseudomonas* readily contaminates the hands of the nursing staff (54 99 106). Often the bedding and urine bottles of these patients are also highly contaminated (54 99 106, 150) and handling them may probably also contaminate the hands.

Cram-negath bacilli do not belong to the normal permanent bacterial flora of the skin and they disappear spontaneously (156, 177). However, even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massive contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100). Since *Pseudomonas* is able to survive and even to grow

Cases of urinary tract infection with *Pseudomonas* have been described in patients with indwelling catheter and in operated patients (55 106 108 130). Animal experiments have shown that obstruction or foreign bodies in the urinary tract predispose to infection even in the presence of a fully normal antibody level of the body (111).

The susceptibility to bacillary infections often seen in patients with leucæmia and aplastic anaemia and persons receiving radiotherapy or x ray treatment (15 19 25 56, 75 166 167 176) is held to be largely a result of lowering of the general resistance of cells and depression of antibody formation by irradiation as well as by antimetabolites and cortisone (21 67 115 177).

Patients with chronic pulmonary processes and fibrosis of the pancreas have been observed to be sensitive to *Pseudomonas* infection (42, 72, 167 176). The basic disease in these cases probably lowers the resistance of the bronchial mucosa, rendering it easier for possible pathogenic pharyngeal bacteria to attack the bronchi (29 62 91 91).

It is a generally accepted opinion that antibiotic therapy predisposes to *Pseudomonas* infections (15 175 180). The basis may be that colonization is facilitated by disappearance of the sensitive normal mucosal flora and that, at least in the newborn, antibody formation is weaker owing to disappearance of the innocent intestinal flora of maternal origin (8 144 177). Experiments in vitro have also indicated that growth of some *Pseudomonas* strains is stimulated by tetracyclines or chloramphenicol (145).

Infections Due to *Pseudomonas*

The *Pseudomonas* may produce both localized infections as well as systemic infection. The incubation time is 5–7 days (116, 155). When the infectious agent directly attacks the meninges (77) or the trachea (125 159) incubation requires only 1–2 days.

Infections of the external auditory canal and the middle ear are typical *Pseudomonas* infec-

tions (55 123 165). However it is rarely encountered as the causative agent in acute otitis media being more common in chronic processes in the ear (30 55 87 122, 155). It can cause infections of the eye of various kinds, from conjunctivitis to panophthalmitis (18, 30, 55). Burns and operation wounds may become infected (15 30 55 99 177) and likewise the umbilical stump of the newborn infant (92, 143, 155). Associated with *Pseudomonas* infections there are a great variety of skin symptoms, being evidently secondary signs of the septicaemia and manifesting either as metastatic foci or toxic reactions (56).

The *Pseudomonas* has been found to give rise to respiratory tract infections of various kinds and degrees. Cases have been described of purulent rhinitis (113, 155) bronchitis, pneumonia, abscess of the lungs and empyema (54, 143, 155). It has been found to cause localized infectious foci on the pharyngeal mucosa and in the parotid glands (39 55) as well as infections of the lower alimentary tract, diarrhoea of varying degree, and peritonitis (30 54 55 94 143, 155). It has also been responsible for urinary tract infections (30 55 177) and meningitis (30, 55, 77).

All of the above conditions may lead to septicaemia to which the newborn infant in particular is susceptible (55, 56 118 143). Septicaemia has been found to develop especially on the base of infected operation wounds, burns, urological operations and umbilical infection (45 81 113, 172) but it can also occur without a clearly evident primary focus (55). Septicaemia due to *Pseudomonas*, like bacteraemia from other gram-negative bacilli, may be accompanied by endotoxin shock (172).

In the published series of *Pseudomonas* infections the recovery and mortality incidences have varied over a wide range. They have doubtless been influenced by marked differences in the susceptibility to infection of the various patient groups as well as by fairly great differences in treatment. However mortality is almost without exception high in the more severe forms of disease, such as peritonitis, meningitis and septicaemia, with incidences ranging from 20 to nearly

100 / (50, 55 77 155, 172) Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at about 80 / when endotoxin shock was present, and at 20 / in other cases (172).

Histologically the typical change in *Pseudomonas* infections is a diffuse acute vasculitis, with abundant bacteria on the vascular walls, and haemorrhages, thromboses and necroses in the adjacent tissues (55).

Epidemics Caused by *Pseudomonas*

In the non-hospital population the *Pseudomonas* is rarely the causative agent in primary infectious processes (55, 77 87 102, 129 177), and epidemics are also of rare occurrence except in hospitals. However there are reports of diarrhoea epidemics due to infected milk or well water (47 145).

In hospitals, on the other hand, *Pseudomonas* has been the cause of epidemics, some of which have been quite large, and these hospital infections have increased considerably within the last two decades (19, 50 56, 55 45). They have been quite numerous in newborn and premature nurseries (10 21 22, 39 47 69, 72, 89 92, 94 115 116, 128, 132, 165, 167 178) and in urological and burns units (30, 81 99 106 108, 109 111 150 167). They have also been reported from other units (17 18 43 127 158, 159, 167 176).

For the onset of hospital infection with *Pseudomonas* there are certain preconditions, which were brought out by Wahba in his investigation in 1965 (167). Using combined pyocine and serological typing method he studied the *Pseudomonas* strains in different kinds of hospital wards. Where the incidence of infection was low the isolated strains were often of various types presumably brought in by patients and the infections were in great extent nosocomial. This situation he found in the eye, ear and surgical wards, whereas in the urological, burns and paediatric units a certain strain often was dominant for some length of time and an

epidemic of clearly this type prevailed in the ward.

An essential factor in the onset of an epidemic appeared to be the number of infection-susceptible patients in the ward. When they were few in number the *Pseudomonas* spread slowly and the various cases were caused by different types of the micro-organism. When there were many patients of this kind, some given strain became predominant and was the cause of numerous cases of infection in the course of weeks or months.

Wahba summarized the situation by stating that whenever highly susceptible patients came in contact with heavy disseminators of the organism, cross-infection was common (167).

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Gram-negative bacilli do not belong to the normal permanent bacterial flora of the skin and they disappear spontaneously (156, 177). However even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massive contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100). Since *Pseudomonas* is able to survive and even to grow

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omycin and bacitracin (30, 123). Sensitivity to chloramphenicol, tetracycline and streptomycin varies, but a rapid development of resistant strains has been observed (15, 30). This is probably due to the ability of gram-negative bacilli to acquire resistance against a drug, or even a number of drugs simultaneously by transferring resistance-carrying genetic factor from one strain to another (26, 170).

Good results have often been achieved in *Pseudomonas* infections with polymyxin and with colistin, an antibiotic drug of the same type (30, 55, 77, 123, 155). However a drawback in the use of polymyxin is its rather high toxicity while part of the *Pseudomonas* strains have been found to develop resistance towards the less toxic colistin (27, 30, 151). The combination of chloramphenicol or tetracycline with polymyxin or colistin may nevertheless intensify their effect (74).

Two fairly new antibiotics, gentamicin (20, 27, 75, 157) and the semisynthetic penicillin derivative carbenicillin (28), have also proved effective in *Pseudomonas* infections. A synergistic effect can possibly be obtained by combined therapy using these two drugs, or one of them with other antibiotics (28). In vitro tests, however have already shown that some *Pseudomonas* strains develop resistance to gentamicin (20).

For topical treatment, not only antibiotics but also a number of other antibacterial agents, including chlorhexidine (51, 125) silver nitrate (52, 101) dilute acetic acid (126), and furazolidone (58), have been used with fairly good results.

In the case of patients with immunoglobulin deficiency ordinary and hyperimmune plasma (51, 76, 81) and gamma-globulin (81, 88, 157) have been used in the treatment and prophylaxis of *Pseudomonas* infection. In the future it may be possible to protect susceptible patient groups by vaccination (4, 6).

It is obvious that an essential requirement for the prevention of hospital epidemics of *Pseudomonas* infection is meticulous hospital hygiene that takes into consideration the special nature of this genus of bacilli (30, 89, 175). It appears to be of utmost importance to keep the hospital equipment and supplies free of the infective agent. A definitely reliable result can apparently be attained only through sterilization by autoclaving or with ethylene oxide (176). In the cleaning of equipment that cannot be sterilized in this manner fairly good results have been obtained with, among other substances, sodium hypochlorite (21, 175), iodophores (69), dilute acetic acid (9, 45) glutaraldehyde (65, 71, 156) and chlorhexidine (175).

in the hospital environment at room temperature if some humidity and organic material is available (16 70 103 111 117) a small amount of bacteria may through the medium of fomites lead to an ultimately massive infection.

Transmission by equipment and supplies By various methods of typing, epidemic strains of *Pseudomonas* have been demonstrated in hospital equipment and medical supplies, and the epidemic has subsided when the source of infection has been destroyed (17 18 22, 159) Although in very many of the earlier studies it was not possible, in the absence of a typing method, to demonstrate that the *Pseudomonas* isolated from the equipment was of the epidemic type: the ceasing of the epidemic after disappearance of the source of infection indicates that this probably was the case in also these instances (69 114 165 178) It is presumable that contaminated hospital equipment and nursing supplies have been the most significant factor in the development of most epidemics.

Among hospital equipment particularly susceptible to *Pseudomonas* colonization are all items that stay moist or are difficult to clean. The organism has been isolated from oxygen equipment (43 89 104) suction apparatuses (22 89 96 139) nebulization equipment (15 89 92 110 111 112 134) incubators (21 89 92, 96 146) resuscitation equipment and respirators (89 125) various parts of anaesthesia equipment (65 153 179) and heart lung machines (83)

Spread of the infection has been observed to have occurred by means of various contaminated medicines (19 117 121 128) bandaging material (158) and water that was believed to be sterile (89 159 178)

It has also been observed that various disinfectants may be infected with *Pseudomonas* sometimes quite heavily Quaternary ammonium compounds are in themselves poorly effective against this organism (175 177) and their action is lowered by numerous substances such as proteins, cellulose and cork (98 120 127) to such an extent that the solution or the material stored in it may become contaminated (127) The tannin in bark corks has been observed to lower the

effect of also chlorhexidine (93, 109) so that instead of the expected disinfection there may have occurred transmission of infection by the solution.

Hexachlorophene which is in wide use for the disinfection of the hands, also possesses a relatively weak action against *Pseudomonas* (85, 100) and the organism has been encountered in soaps (11) hand creams (85) and shampoos (17) containing hexachlorophene and in hexachlorophene dispensers (89)

Kitchen sinks, cupboards and dishes have been found to be contaminated with *Pseudomonas* (99 148) and may have been responsible for spreading of the infection.

Transmission by air and dust. Although *Pseudomonas* is not properly a dust bacterium, it appears to be able to survive in the hospital environment for long periods after once entering it (70 99) It has not been encountered ordinarily in hospital air (45 107 168) but during epidemics it has been present even in large numbers, in samples of the air (99 116 150 176) Air humidifiers may also promote transmission of the organism by air (11 45)

Carriers of Pseudomonas. Carriers of *Pseudomonas* in the hospital staff probably play but a small part in the onset and spread of hospital epidemics, since such carriers have been quite few in number even during epidemics (18, 22 99) On the other hand faecal carriers among the patients have been found to be probable disseminators of *Pseudomonas* (148) This possibly is ascribable to contamination of hands or equipment in connection with care and treatment, and is less likely to occur when the bacteria carriers are healthy members of hospital personnel.

Treatment and Prophylaxis of *Pseudomonas* Infection

Pseudomonas organism has generally been found to be highly resistant to the commonly used antibiotics, as penicillin, ampicillin, eryth

polymyxin and bacitracin (50, 123). Sensitivity to chloramphenicol, tetracycline and streptomycin arises, but a rapid development of resistant strains has been observed (15, 50). This is probably due to the ability of gram-negative bacilli to acquire resistance against drug, or even a number of drugs simultaneously by transferring a resistance-carrying genetic factor from one strain to another (26, 170).

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Object of Investigation

The investigation presented here was undertaken with the object

1) to study the occurrence of the *Pseudomonas* bacillus in a paediatric surgical unit treating children under 2 years of age

2) to study the relationship between *Pseudomonas* colonization and *Pseudomonas* infections, and their significance for the surgical paediatric patient and

3) to clarify the routes and modes of transmission of *Pseudomonas* infection.

Material and Methods

Material

The present investigation was carried out during the 12 month period from October 1 1962 to September 30, 1963 in the surgical unit of the Children's Hospital of the Helsinki University Central Hospital. This unit has 22 beds for children under 2 years of age. During 1962 the impression had been gained clinically supported by numerous findings of *Pseudomonas* infection in intubated patients (132) that there was *Pseudomonas* epidemic of hospital infection type in the unit. Opinions varied concerning the importance that should be attached to the epidemic, the prevailing opinion being that the *Pseudomonas* was saprophytic of no noteworthy consequence for the patient.

For this reason, *Pseudomonas*-colonized children were not isolated either in the ward or in the operation room. This was the situation during the first three months of the present study from October 1 to December 31 1962. After the latter date efforts were made to prevent spread of the infection by isolating the patients in whom *Pseudomonas* bacilli were found and by intensifying of the cleaning and sterilization of the equipment used in the care and treatment of these patients.

During the period of this investigation a total of 513 surgical patients were hospitalized in the unit. They varied in age from a few hours to about 2 years. Samples were taken on admission from each patient: nose and throat for bacterial culture. This was repeated once or more times in the case of children suspected of being particularly susceptible to infection, such as patients in poor condition and newborn infants. Urine samples from urological patients were examined

twice a week. Upon onset of any signs of infection in patient samples pertinent to the symptoms were immediately taken. A total of 2,771 bacterial culture samples were examined.

Nose and throat swabs were taken six times from the surgical staff and four times from the ward personnel. These samples totalled 511.

Samples for bacterial culture were taken at intervals of 1-2 months from part of the equipment and environment in the operating room and the ward. Other equipment was sampled according to use and when there was particular reason to suspect contamination. The air was examined eight times in the operating room and twice in the ward. A total of 1072 samples were examined.

Methods

Sample taking and culture Samples from the nose and throat and of pus were taken with dry sterile cotton swab. All the urine samples were drawn by catheter. A sample of bronchial mucus was taken from the sterile glass connecting tube when the bronchial toilette was being done. In intubated cases a sample was taken from the lungs for bacterial culture, as described by Rantaaalo and Hjelt (132).

The samples from the hospital equipment and environment were taken mostly with sterile dry cotton swabs. Swabs dipped in sterile saline solution were used for a part of the dust samples from furniture and floors. In the case of suction bottles, oxygen equipment, incubators, nebulizers, respirators and anaesthesia equipment a number of samples were taken from different parts of the fomite, particularly from areas that are difficult

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to clean or that stay moist. For collection of airborne bacteria, blood agar dishes 9.5 cm in diameter were placed in all the rooms and kept exposed for 2-12 hours, usually during the busy working hours.

Culture of the samples was carried out in the hospital's laboratory. Samples of urine were allowed to drip directly from the catheter onto blood agar dishes. The faeces samples were grown on SS agar (Difco) and Drikalsky agar and in selenite tubes. The bacterial cultures from all the other samples were made on blood agar in liver broth or in semisolid nutrient agar. The cultures were personally examined by the writer after 24 hours incubation, and negative cultures were incubated for a further 24 hours.

Identification: A tentative identification of the bacterial growth was made in the hospital's laboratory on the basis of staining appearance of the colonies, haemolytic capacity, pigment formation and odour. Preparatory biochemical examinations were made of all gram negative rod

bacteria in triple sugar iron-agar, urea agar and motility tubes. All the strains obtained were then sent to the State Serum Institute, Helsinki, where the final species determination was carried out.

As *Pseudomonas* bacilli were regarded all gram negative rod bacteria provided they used no sugars other than possibly glucose, were motile, formed a green pigment, liquefied gelatin, and did not produce indole. Other gram negative rod shaped organisms were identified according to the formula of Kauffmann (80).

All phosphatase-positive *Staphylococcus* were also tested for the production of coagulase, and positive strains were regarded as *Staphylococcus aureus*.

Statistical analysis: In statistical comparisons of the results the Chi analysis was used as a four squares test (3). The difference was considered to be highly significant when $P < 0.1\%$, significant when $P < 1\%$, and almost significant when $P < 5\%$.

Results

Occurrence of *Pseudomonas* during the Present Study

1 Patients

Time distribution. *Pseudomonas* bacilli were isolated from 202 of the 2,771 samples taken from patients in the surgical unit of the Children's Hospital. The 202 samples were from 53 patients, who comprised 10.5% of the 513 patients under treatment in the unit during the period of the present study.

Table 1 and Fig. 1 show the monthly distribution of the patients found to be colonized with *Pseudomonas*. The largest number of cases occurred at the beginning and the end of the period studied. In October-November-December 1962 and August-September 1963, 57 (16%) of the patients under treatment were colonized, whereas there were only 16 colonized patients (4%) during the intervening seven months. The difference between these numbers is statistically highly significant.

Deaths during the studied period and *Pseudomonas* colonization. Seventeen of the 53 *Pseudomonas*-colonized patients died. In 16 of these cases the organism was isolated in cultures of lung samples taken at autopsy. In one case the culture from the lung was negative, but *Pseudomonas* had been identified in wound pus during life. The lung culture gave the only positive finding of *Pseudomonas* in 6 cases. With one exception the deaths of *Pseudomonas*-colonized infants were concentrated to the first months and last months of the period studied (Table 1 and Fig. 1). Eleven of 23 colonized children died during the first 5 months, and 6 died of the 30 colonized children who were hospitalized later. The difference is highly significant.

A total of 41 deaths occurred among the 513 patients treated in the surgical unit at the time of this investigation. In 16 of these cases (39% of deaths) the bacterial culture of the lung sample was positive for *Pseudomonas*, as said above. Of the total of 19 children who died during the

TABLE 1. Number of *Pseudomonas*-colonized patients and of deaths among them, as compared to non-colonized patients and all patients, by months.

Year	1962					1963							
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept.	Total
<i>Pseudomonas</i>													
colonized patients	11	7	7	2	1	5	4	0	5	1	5	9	55
Number of deaths	5	3	3	0	0	0	1	0	0	0	2	5	17
Non-colonized patients	17	36	38	49	36	27	37	38	36	43	35	40	460
Number of deaths	3	2	3	5	2	1	1	3	1	4	0	1	24
Total number of													
patients	28	43	45	51	37	32	41	38	39	44	38	49	513
Number of deaths	8	5	6	5	2	1	2	3	1	4	2	4	41

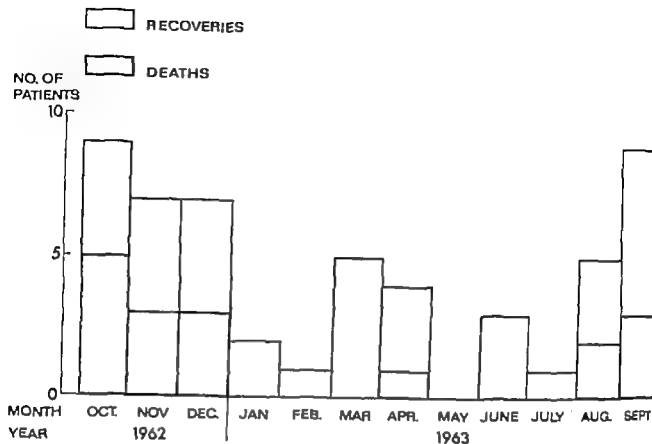


Fig 1 Number of *Pseudomonas*-colonized patients, by months.

first 3 months of this investigation 10 had a *Pseudomonas* positive lung culture while this was the case in only 6 instances among the 23 children who died during the remainder of the study period.

During the same 12 months, *Pseudomonas* was isolated at autopsy from 5 of the 14 infants who died in the premature ward and from 3 of the 20 children who died in the infection ward for children under 2 years. These figures differ significantly from the *Pseudomonas* colonization figures in the paediatric surgical unit studied.

***Pseudomonas* infections** An infection caused by *Pseudomonas* bacilli was diagnosed in 32 children which is equivalent to 6.2% of all the patients treated in the unit. The number of children exhibiting signs of infection was highest during the first 3 months of the study differing almost significantly from the number of cases diagnosed later (Table 2 and Fig 2). On the other hand the incidence of *Pseudomonas* carriers without symptoms was approximately the same

in the two periods studied i.e., 1.2% and 11%, respectively.

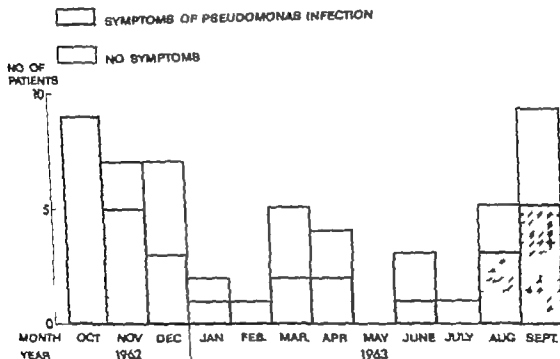
Time of finding of colonization The isolation of *Pseudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit was regarded as a sign that there had been colonization already on admission. Such cases numbered 23 or 19% of all children treated in the unit, if they were approximately evenly distributed throughout the period studied (Table 3 and Fig 3).

All the children who were colonized on admission to the unit either had been transferred directly from the hospital unit or were re-hospitalized after having been there for 2 months at the most.

A finding of colonization with *Pseudomonas* was made in the first 3 months of the study in 23 children or 5.5% of all children in the unit. Samples had not been taken earlier for fear of these children 3 of whom were colonized at birth during the first 3 months of the studied

TABLE 2. Number of *Pseudomonas* infections among the colonized patients, by months.

Year	1962						1963							Total
	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.		
<i>Pseudomonas</i> -colonized patients														
Without symptoms	0	2	4	1	0	3	2	0	2	1	2	4	21	
With symptoms of infection	9	5	3	1	1	2	2	0	1	0	3	5	32	
Newly colonized patients	17	16	36	49	36	27	37	33	36	43	33	40	460	
Total number of patients	56	43	45	51	37	52	41	36	39	44	36	49	513	

Fig. 5. Number of *Pseudomonas* infections among the colonized patients, by months.

and the number of children colonized in the unit was highest during the first 3 months, with a total of 11 children or 11 of 11 children colonized in the unit during that time. During the remainder of the studied period there were only 12 colonized children or 33%. The difference was highly significant. Of the latter 12 children 6 were hospitalized in the unit during

the first part of the stated period and 6 during the last 2 months (Table 3 and Fig. 5).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 260 throat samples taken from the ward personnel and the surgical staff.

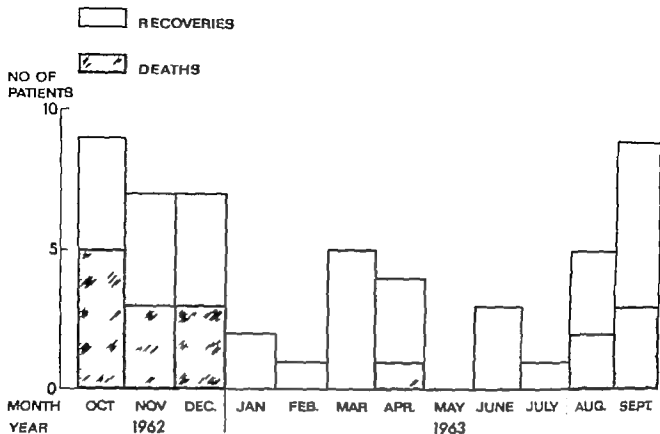


Fig 1 Number of *Pseudomonas*-colonized patients, by months.

first 3 months of this investigation 10 had a *Pseudomonas* positive lung culture while this was the case in only 6 instances among the 22 children who died during the remainder of the study period.

During the same 12 months, *Pseudomonas* was isolated at autopsy from 5 of the 14 infants who died in the premature ward and from 3 of the 20 children who died in the infection ward for children under 2 years. These figures differ significantly from the *Pseudomonas* colonization figures in the paediatric surgical unit studied.

***Pseudomonas* infections** An infection caused by *Pseudomonas* bacilli was diagnosed in 32 children, which is equivalent to 6.2 % of all the patients treated in the unit. The number of children exhibiting signs of infection was highest during the first 3 months of the study differing almost significantly from the number of cases diagnosed later (Table 2 and Fig. 2). On the other hand the incidence of *Pseudomonas* carriage without symptoms was approximately the same

in the two periods stated, i.e. 1.2 % and 4.1 %, respectively.

Time of finding of colonization The isolation of *Pseudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit was regarded as a sign that there had been colonization already on admission. Such cases numbered 23 or 1.9 % of all children treated in the unit, and they were approximately evenly distributed over the period studied (Table 3 and Fig. 3).

All the children who were colonized on admission to the unit either had been transferred directly from other hospital units or were re-hospitalized after having been at home for 2 months at the most.

A finding of colonization with *Pseudomonas* was made later than on the second day in 28 children i.e. 5.5 % of all children under treatment. Samples had not been taken earlier from 5 of these children 3 of whom were under treatment during the first 3 months of the study.

TABLE 2 Number of *Pseudomonas* infections among the colonized patients by months

TABLE 2. Number of patients													
Year	1962						1963						
Month	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Total
<i>Pseudomonas</i> colonized patients													
Without symptoms	0	2	1	1	0	3	2	0	2	1	2	1	21
With symptoms of infection	9	5	5	1	1	2	2	0	1	0	3	5	32
Non-colonized patients	17	16	18	19	16	27	37	38	16	15	33	40	460
Total number of patients	26	23	24	21	17	32	41	38	19	16	38	46	513

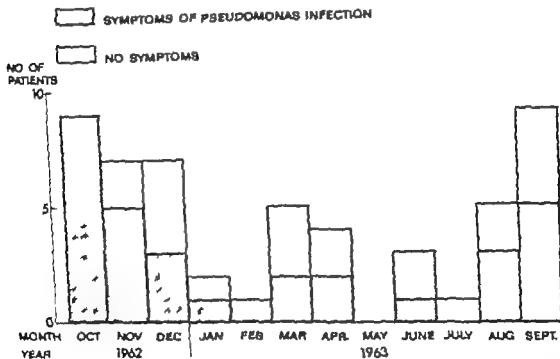


Fig. 1. Occurrence of *Pseudomonas* infections among the colonized patients, by months.

period. The number of children colonized in the unit was highest during the first 3 months, totalling 16 children, or 11% of all children treated in the unit during that time. During the remainder of the studied period there were only 12 colonized children, or 5.5%. The difference is statistically highly significant. Of the latter 12 children 6 were hospitalized in the unit during

the first part of the stated period and 6 during the last 2 months (Table 3 and Fig. 5).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 260 throat samples taken from the ward personnel and the surgical staff.

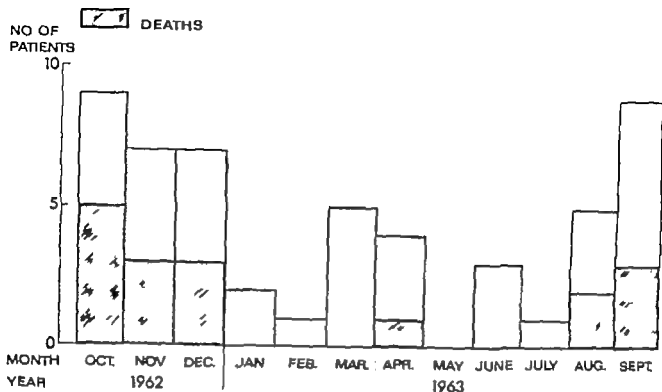


Fig 1 Number of *Pseudomonas*-colonized patients, by months.

first 3 months of this investigation, 10 had a *Pseudomonas* positive lung culture while this was the case in only 6 instances among the 22 children who died during the remainder of the study period.

During the same 12 months, *Pseudomonas* was isolated at autopsy from 5 of the 44 infants who died in the premature ward and from 5 of the 90 children who died in the infection ward for children under 2 years. These figures differ significantly from the *Pseudomonas* colonization figures in the paediatric surgical unit studied.

***Pseudomonas* infections.** An infection caused by *Pseudomonas* bacilli was diagnosed in 52 children which is equivalent to 62 % of all the patients treated in the unit. The number of children exhibiting signs of infection was highest during the first 3 months of the study differing almost significantly from the number of cases diagnosed later (Table 2 and Fig 2). On the other hand the incidence of *Pseudomonas* carriers without symptoms was approximately the same

in the two periods stated, i.e. 1.2 % and 4.1 % respectively.

Time of finding of colonization. The isolation of *Pseudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit was regarded as a sign that there had been colonization already on admission. Such cases numbered 2 or 1.9 % of all children treated in the unit, and they were approximately evenly distributed over the period studied (Table 3 and Fig 3).

All the children who were colonized on admission to the unit either had been transferred directly from their hospital unit or were re-hospitalized after having been at home for 2 months at the most.

A finding of colonization with *Pseudomonas* was made later than on the second day in 28 children i.e. 5 % of all children under treatment. Samples had not been taken earlier from 5 of these children 3 of whom were later treated in the first 3 months of the studied

TABLE 2. Number of *Pseudomonas* infections among the colonized patients, by months

Year		1962						1963						Total
Months	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.		
<i>Pseudomonas</i> infected patients														
Without symptoms	0	2	4	1	0	5	2	0	2	1	2	4	20	
With symptoms of infection	9	5	3	1	1	2	2	0	1	0	3	5	32	
Non-colonized patients	17	36	58	43	56	27	57	58	36	15	5	10	460	
Total number of patients	56	43	45	1	57	32	11	58	50	14	18	19	513	

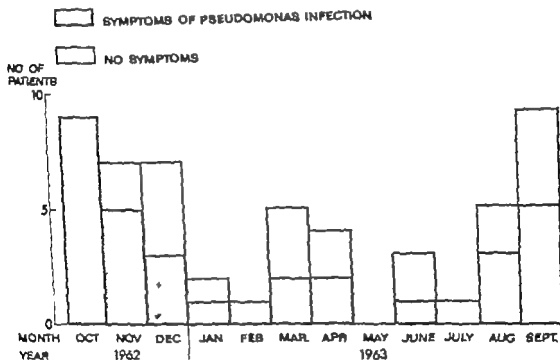


Fig. 2. Occurrence of *Pseudomonas* infections among the colonized patients, by months.

period. The number of children colonized in the unit was highest during the first 3 months, totalling 16 children, or 11% of all children treated in the unit during that time. During the remainder of the studied period there were only 12 colonized children, or 3.3%. The difference is statistically highly significant. Of the latter 12 children, 6 were hospitalized in the unit during

the first part of the stated period and 6 during the last 2 months (Table 3 and Fig. 3).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 260 throat samples taken from the ward personnel and the surgical staff.

TABLE 3 *Pseudomonas*-colonized patients classified according to time of diagnosis and colonization by months

		colonization by months											
Year		1963											
Month		Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	Jun.	July	Aug.	Sept.
<i>Pseudomonas</i> -colonized patients													
Colonized on admission		5	2	2	1	0	3	2	0	0	1	3	5
Colonized later		6	5	6	1	1	2	2	0	0	0	2	1
Non-colonized patients		17	36	38	49	50	27	37	38	56	13	33	40
Total number of patients		56	45	45	61	37	32	41	58	59	14	58	19

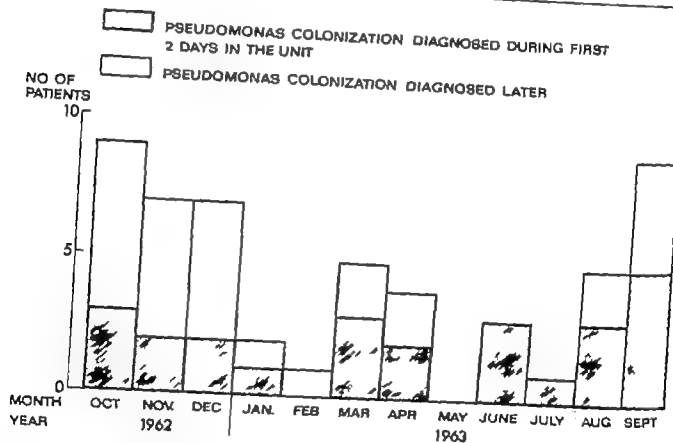


Fig. 3 *Pseudomonas*-colonized patients classified according to time of diagnosis of colonization by months

C Samples from the Environment Equipment and Air

The environments and fomites in the ward unit and the operating unit examined for *Pseudomonas* and the time of each sample-taking are stated in Table 1. Heavy contamination of the

equipment and environment was revealed during the first 3 months of the investigation period. At this time *Pseudomonas* was found in many items in the operating and the ward units. In the first mentioned the organism grew from samples taken from the rubble of an anesthesiologist's

TABLE 1. Bacterial studies of hospital equipment and on material in the hospital as a whole during the period 1st July 1962 to 31st June 1963

Object examined	On	1962												Total number of samples	Number of <i>Pseudomonas</i> positive
		Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct		
Operating unit														99	3
Anaesthetic machines	+													72	0
Other equipment	-													150	0
Phase plates, pol. discs															
Collectors														38	1
Sea spray	+													20	0
Substrates	-														
Brushes															
Hand														67	1
Inoculators	-													12	0
Nebulizers	-													11	0
Oxygen humidifiers	-													15	0
Suction apparatuses	-													22	0
Suction catheters	-													11	0
Respirator	-													1	1
Glass bottles for drip-feeding														10	0
Feeding tubes	-													31	0
Penicillin	-													1	0
Head cream jars															
Stomach aspirates															
Patient rooms	+													71	9
St. ice rooms	-													15	1
Kitchens	+													17	3
Other rooms	-													25	0
Bathrooms	-													44	2
Brushes															
A. trypsin	+													29	1
Examination room	-													31	0
Sliding room	+													31	2
Floor brushes	-													17	0
Room paths	-													11	0
Floor (slat)	-													15	0
for (settling plates)															
Ward	-													18	0
Operating unit	-													176	0
Number of samples examined	48	185	81	83	56	19	83	27	111	158	87	56		1072	
Number <i>Pseudomonas</i> positive	0	11	1	1	0	5	0	0	0	0	1	5		22	

- = No growth of *Pseudomonas* in culture.

+ = Growth of *Pseudomonas* in culture. Exponent indicates the number of samples positive for *Pseudomonas*.

TABLE 3 *Pseudomonas*-colonized patients classified according to time of diagnosis of colonization by months

Year	1962						1963						
Month	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Total
<i>Pseudomonas</i> colonized patients													
Colonized on admission	3	2	2	1	0	3	2	0	3	1	5	5	3
Colonized later	6	5	5	1	1	2	2	0	0	0	2	1	23
Non-colonized patients	47	56	58	111	56	27	37	58	56	15	53	10	160
Total number of patients	56	63	65	61	57	32	41	58	59	14	58	19	512

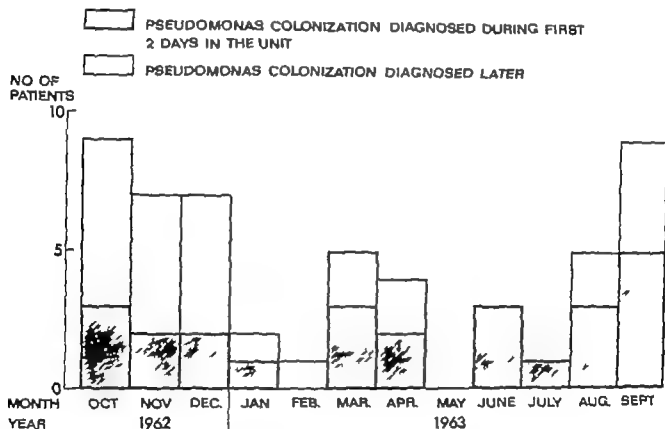


Fig 3 *Pseudomonas*-colonized patients classified according to time of diagnosis of colonization, by months.

C Samples from the Environment Equipment and Air

The environments and fomites in the ward unit and the operating unit examined for *Pseudomonas* and the time of each sample-taking are stated in Table 4. Heavy contamination of the

equipment and environment was revealed during the first 3 months of the investigation period. At this time *Pseudomonas* was found in many items in the operating and the ward unit. The first mentioned organism grew from samples taken from the rubber tube and tube connector of an anaesthesia machine and from the mouth

and 3 during the last 2 months of this study. Among the 8 non-colonized newborn there were 16 deaths, which were fairly evenly distributed over the study period.

Time of colonization. *Pseudomonas* bacilli are found in all neonates during the first 2 days in the surgical unit (Table 6 and Fig. 1). This was 5.8% of the newborn infants hospitalized, and their distribution over the studied period was fairly even. They all were over 2 days old on admission and only 2 of them had been sent to the surgical unit immediately from the newborn nurseries of different hospitals, while 1 had been transferred from various other units of the same hospital.

A later finding of *Pseudomonas* was made in 20 infants, in 19 of all infants admitted as newborn. In most cases these patients had arrived directly from newborn nurseries and only 2 had been transferred from other hospitals. Suspects had not been taken on admission from

16 patients, 2 of whom were under treatment during the first 3 months of this study.

The number of newborn infants who had become colonized with *Pseudomonas* while in the surgical unit was highest during the first 3 months of this study; these 15 patients made up over a third of all the newborn in the unit at the time. During the remainder of the studied period only 7 (10%) of those admitted as newborn became colonized while in the unit. The difference in the incidences between the two periods is highly significant.

Various factors influencing colonization. The number of *Pseudomonas*-colonized newborn girls was over twofold that of newborn boys, whereas the total series of 101 newborn infants contained 2 boys more than girls (Table 7). About a fifth of the colonized and about a tenth of the non-colonized neonates were in the premature weight range. The highest incidence of *Pseudomonas* colonization was seen among the newborn

TABLE 6 Time of diagnosis of *Pseudomonas* colonization in the neonatal patients during the first 3 months and the following 9 months of the present study

	Oct. 1 - Dec. 31 1962	Jan. 1 - Sept. 30, 1963	Total
<i>Pseudomonas</i> colonized			
Colonies first diagnosed during the first 2 days in hospital	1	5	6 (5.8%)
Colonization diagnosed later	15	7	20 (19%)
Non-colonized	19	59	8
Total number of neonates examined	35	71	106

TABLE 7 Relationship of *Pseudomonas* colonization to sex, birthweight and presence of anomalies in the neonatal patients

	<i>Pseudomonas</i> -colonized	Non-colonized	Total
Boys	8	45	53
Girls	18	35	51
Birth weight > 3.5 kg.	21	70	91
Birth weight 2 kg. or less	5	8	13
Yes or anomaly of the digestive tract	20	24	44
Other anomaly	2	53	35
No anomaly	4	21	25
Two or more anomalies	11	11	22

of the washbasin drain in the patients waiting room. In the ward unit the organism was isolated in the first 3 months from edges of the kitchen sink drain and from a kitchen brush, from one incubator used for newborn patients, and from the mouth of the washbasin drain in four of the patient rooms. At the very beginning of the fourth month of investigation *Pseudomonas* cultures were obtained from glass bottles used for children's continuous drip-feeding.

Pseudomonas organisms were obtained later only from bathtubs and washbasins in the isolation rooms of colonized children, in addition to which the kitchen sink was again found to be contaminated at the end of the investigation period.

The settling plates for collection of air borne bacteria did not yield any growth of *Pseudomonas*.

Occurrence of *Pseudomonas* in Different Types of Patient Groups

The series of patients studied can be divided into three groups: patients admitted as newborn at less than 28 days of age; urological patients,

and other patients. The 26 infants in the *Pseudomonas* series who were admitted as newborn made up nearly a half of the colonized patients. There were 8 urological cases in the *Pseudomonas* series. The remaining 19 colonized patients were of different ages and had been admitted for various reasons, forming no distinct group.

Table 5 presents the monthly distribution of all patients and of *Pseudomonas*-colonized patients in each of the above groups.

A Patients Admitted as Newborn

Occurrence of *Pseudomonas* colonization and relationship to mortality: *Pseudomonas* colonization was found in 26 of the 104 neonate patients treated in the unit, or in 25 per cent (Table 5). The incidence among the newborn was particularly high in the first 3 months of the study when the organism was isolated from 14 of the 33 neonates under treatment. During the following 9 months, only 12 of the 71 infants admitted as newborn were found to be colonized. The difference between these figures is statistically significant.

Deaths in the group of *Pseudomonas*-colonized infants who had been admitted as newborn totalled 13, 9 occurring during the first 3 months

TABLE 5 Number of neonate urological and other patients treated in the paediatric surgical unit and occurrence of *Pseudomonas* colonization in each group by month

Year	1962					1963								
Month	Oct.	Nov	Dec.	Jan.	Feb.	Mar	Apr	May	June	July	Aug	Sept.	Total	
Neonate patients of whom <i>Pseudo-</i> <i>monas</i> -colonized	12	9	12	8	5	7	11	9	6	11	7	7	104	
	6	4	6	0	0	2	4	0	1	1	2	2	26	
Urological patients of whom <i>Pseudo-</i> <i>monas</i> -colonized	5	1	1	2	2	1	1	0	1	0	3	5	22	
	3	1	0	0	1	1	0	0	0	0	1	1	8	
Other patients of whom <i>Pseudo-</i> <i>monas</i> -colonized	39	35	52	41	50	24	29	29	32	35	28	37	587	
	1	2	2	1	0	3	0	0	2	0	2	6	19	
Total number of patients	56	45	45	61	57	32	41	38	39	44	38	19	513	
of whom <i>Pseudo-</i> <i>monas</i> -colonized	9	7	7	2	1	5	4	0	3	1	5	9	53	

and 3 during the last 2 months of this study. Among the 78 non-colonized newborn there were 16 deaths, which were fairly evenly distributed over the study period.

Time of colonization. *Pseudomonas* bacilli were found in 6 neonates during the first 2 days in the surgical unit (Table 6 and Fig. 3). This was 5.8% of the newborn infants hospitalized, and their distribution over the studied period was fairly even. They all were over 2 days old on admission, and only 2 of them had been sent to the surgical unit immediately from the newborn nurseries of different hospitals, while 4 had been transferred from various other units of the same hospital.

A later finding of *Pseudomonas* was made in 20 infants, in 19 of all infants admitted newborn. In most cases these patients had arrived directly from newborn nurseries and only 2 had been transferred from other hospital units. Samples had not been taken on admission from

4 patients, 2 of whom were under treatment during the first 3 months of this study.

The number of newborn infants who had become colonized with *Pseudomonas* while in the surgical unit was highest during the first 3 months of this study; these 13 patients made up over a third of all the newborn in the unit at the time. During the remainder of the studied period only 7 (10%) of those admitted as newborn became colonized while in the unit. The difference in the incidences between the two periods is highly significant.

Various factors influencing colonization. The number of *Pseudomonas*-colonized newborn girls was over twofold that of newborn boys, whereas the total series of 101 newborn infants contained 2 boys more than girls (Table 7). About a fifth of the colonized and about a tenth of the non-colonized neonates were in the premature weight range. The highest incidence of *Pseudomonas* colonization was seen among the newborn

TABLE 6 Time of diagnosis of *Pseudomonas* colonization in the neonatal patients during the first 3 months and the following 9 months of the present study

	Oct. 1 - Dec. 31 1962	Jan. 1 - Sept. 30, 1963	Total
<i>Pseudomonas</i> colonized			
Colonization diagnosed during the first 2 days in hospital	1	5	6 (5.8%)
Colonization diagnosed later	13	7	20 (19%)
Non-colonized	19	50	78
Total number of neonates passed to	35	71	106

TABLE 7 Relationship of *Pseudomonas* colonization to sex, birthweight and presence of anomalies in the neonatal patients

	<i>Pseudomonas</i> -colonized	Non-colonized	Total
Boys	8	45	53
Girls	18	33	51
Birthweight over 2.5 kg	21	70	91
Birthweight 2.5 kg or less	5	8	13
Severe anomaly of the digestive tract	20	21	41
Other anomaly	2	33	35
No anomaly	4	21	25
Two or more anomalies	11	11	22

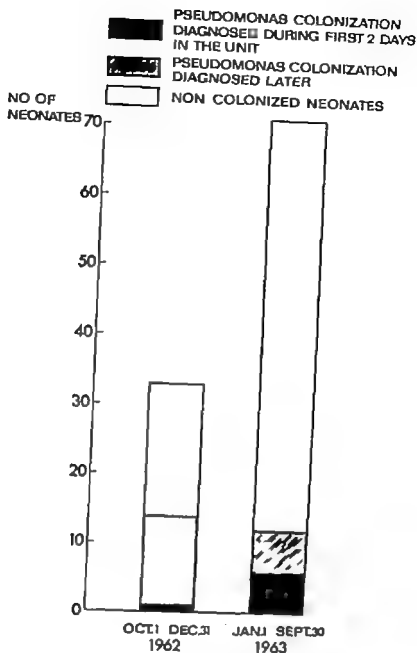


Fig 4 Time of diagnosis of *Pseudomonas* colonization in patients admitted as newborn during the first 3 months and the following 9 months of the present study

infants who were undergoing operation for severe anomaly of the digestive tract, almost half of them yielding cultures of the organism.

The following conditions were regarded as severe digestive tract anomalies: oesophageal atresia or stenosis of the small intestine, ruptured omphalocele, and severe Hirschsprung's disease. Apart from minor anal anomalies, there were only 2 cases of true atresia of the anus, and *Pseudomonas* was not found in any of these 10 pa-

tients. A very high frequency of colonization was found among newborn infants operated on for oesophageal atresia: they made up half of the colonized newborn, and one half of the patients with oesophageal atresia were infected with *Pseudomonas* (Table 8). The number of colonized patients with atresia of the oesophagus differs highly significantly from the number of other colonized neonates, whereas the difference in number between colonized patients with inter-

TABLE 8. Distribution of the neonatal patients by diagnosis, and occurrence of *Pseudomonas* colonization in each diagnosis group

Diagnosis	<i>Pseudomonas</i> -colonized	Non-colonized	Total
Atresia oesophagi	15	10	25
Fistula oesophagogastrica	1	0	1
Atresia superioris duodeni, ilei	1	10	11
Omphalocele ruptured	1	4	5
Vib. Hirschsprung	1	0	1
Atresia superioris anales	0	10	10
Malrotation	0	2	2
Stenosis pylori	2	6	8
Hernia diaphragmatica	0	5	5
Pneumothorax	1	1	2
Hydrocephalus	1	3	4
Poliomyelitis	1	6	7
Other operated patients	0	15	15
Patients under examination	1	6	7
Total number of neonatal patients	26	79	105

tural trauma and other colonized neonates was not significant.

Relationship between Pseudomonas colonization and length of hospitalization. The newborn infants with oesophageal or intestinal atresia or with omphalocele formed fairly uniform group with respect to type of treatment and prognosis but the average length of hospitalization of the *Pseudomonas*-colonized infants was longer than that of the non-colonized. In the case of 20 colonized newborn it was 34 days (range 3-144 day) while for 24 non-colonized newborn it was 18 day (range 1-54 days). The length of hospitalization was less than 100 day.

In the case of 8 infants who died in the colonized group and of 6 who died in the non-colonized group. When these last day of treatment are included the average length of hospitalization of colonized neonates was 50 day and that of non-colonized 22 days. The difference has no statistical significance because of the wide dispersion of the number of day in hospital in the group of *Pseudomonas*-colonized neonates.

Pseudomonas infections. In the group of infants admitted to the surgical unit as newborn, 17 of the 26 found to be colonized with *Pseudo-*

monas had symptoms of infection (Table 9). Ten of these children were under treatment in the first 3 months of the present study and all 10 became colonized with *Pseudomonas* and developed symptoms during hospitalization. In the following 9 months symptoms of *Pseudomonas* infection were seen in 7 newborn, 3 of whom were found to have the infection already on admission.

The most common symptom was pneumonia, which was diagnosed in 10 infants. Six of these cases occurred during the first 3 months of this study. The diagnosis was based in 6 cases on cultures of bronchial mucus and clinical symptoms of pneumonia during life, and in the other cases on autopsy findings alone. Autopsies revealed also 3 cases of bronchitis, all of them during the first 3 months.

The manifestation next in frequency was focal infection. Wound infection occurred in 5 patients, 4 of whom were treated in the first 3 months. Two patients had several suppurating wounds, and in 4 cases suppuration caused dehiscence of the wound. In 2 cases the cultures from pus yielded no other bacteria, but *Pseudomonas* was predominant. Conjunctivitis occurred in 3, un-

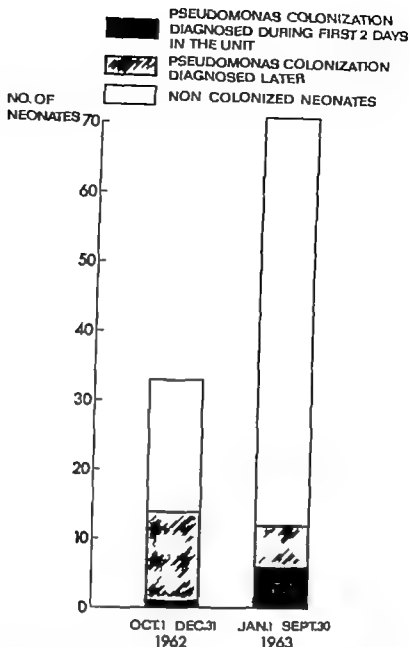


Fig 4 Time of diagnosis of *Pseudomonas* colonization in patients admitted as newborn during the first 3 months and the following 9 months of the present study

infants who were undergoing operation for every anomaly of the digestive tract, almost half of them yielding cultures of the organism.

The following conditions were regarded as severe digestive tract anomalies: oesophageal atresia or stenosis of the small intestine, ruptured omphalocele and acute Hirschsprung's disease. Apart from minor anal anomalies, there were only 11 cases of true atresia of the anus, and *Pseudomonas* was not found in any of these 10 pa-

tients. A very high frequency of colonization was found among newborn infants operated on for oesophageal atresia: they make up half of the colonized newborns and over a half of the patients with oesophageal atresia were infected with *Pseudomonas* (Table 8). The number of colonized patients with atresia of the oesophagus differs highly significantly from the number of other colonized neonates, whereas the difference in number between colonized patients with atresia

TABLE 10. Relationship of mortality to *Pseudomonas* colonization and to inflammatory changes observed at autopsy in the neonate patients during the first 3 months and the following 9 months of the present study

	Oct. 1 - Dec. 31 1962			Jan. 1 - Sept. 30, 1963				Total	Total
	<i>Pseudo-</i> <i>monas</i> colonized	Non- colonized	Total	<i>Pseudo-</i> <i>monas</i> colonized	Non- colonized	Total	<i>Pseudo-</i> <i>monas</i> colonized	Non- colonized	Total
Total number of neonate patients	14	19	33	12	20	32	26	78	104
Number of deaths	9	5	14	4	11	15	15	16	29
Finding of infection at autopsy	7	2	9	4	5	9	11	5	16

- RECOVERIES
 DEATHS WITH AUTOPSY FINDING OF INFECTION
 DEATHS WITHOUT AUTOPSY FINDING OF INFECTION
 PS+ PSEUDOMONAS COLONIZED NEONATES
 PS- NON COLONIZED NEONATES

NO OF NEONATES

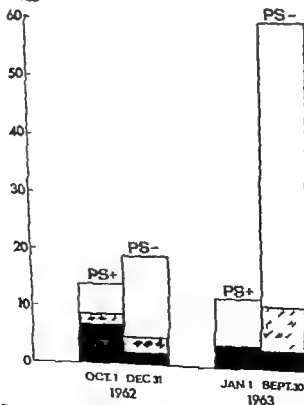


Fig. 5. Relationship of mortality to *Pseudomonas* colonization and to autopsy findings of infection in patients admitted as newborn during the first 3 months and the following 9 months of the present study

TABLE 9 Various forms of *Pseudomonas* infection occurring among the neonate patients during the first 3 months and the following 9 months of the present study

	Oct. 1 - Dec 31 1962	Jan. 1 - Sept. 30, 1963	Totals
Total number of patients admitted as newborn	53	71	104
Number of <i>Pseudomonas</i> -colonized	14	12	26
Number with symptoms of <i>Pseudomonas</i> infection	10	7	17
Symptoms evident on admission	0	3	3
Clinical picture			
Pneumonia	6	4	10
Bronchitis	3	0	3
Septicaemia	1	0	1
Peritonitis	3	0	3
Wound infection	4	1	5
Umbilical infection	2	0	2
Conjunctivitis	1	2	3
Urinary tract infection	1	0	1
Abscess	0	1	1

Pseudomonas was considered to be the infective agent when definite local symptoms of infection were supported by a bacterial culture from the site of infection, in which *Pseudomonas* was the predominant micro-organism. The diagnoses of peritonitis, septicaemia, bronchitis and 4 cases of pneumonia were based on the findings at autopsy.

bilical stump infection in 2, and a cutaneous abscess at the site of medical injection in one newborn.

Peritonitis was diagnosed in 3 infants who underwent laparotomy during the first 3 months studied. All of them had symptoms of peritonitis during life, bacterial cultures made from the faeces in 2 of the cases yielded *Pseudomonas*, and autopsy showed in all 3 cases distinct peritonitic changes, greenish pus in the abdominal cavity and *Pseudomonas* growing from cultures of samples from the lungs.

A case of septicaemia verified at autopsy occurred in the first 3 months, when there also was a case of urinary tract infection due to *Pseudomonas* in a previously catheterized infant.

The 29 newborn admissions who died during the studied period included 11 of the 17 infants with a *Pseudomonas* infection. Only one patient with pneumonia recovered from the infection of the other infected patients who recovered 2 had had conjunctivitis and one patient each had had skin abscess, wound infection and urinary tract infection.




Autopsy findings of colonization and infection with Pseudomonas. Cultures of lung samples taken at the autopsies of 29 infants who had been admitted to the surgical unit as newborn showed growth of *Pseudomonas* in 13 cases (Table 10 and Fig. 5). Histological evidence of infection was found in 11 of these infants, while such changes were present in only 5 of the 16 infants whose lung culture at autopsy did not yield *Pseudomonas*. Thus the incidence of infection in the former group was twofold in comparison to the latter group.

Details of the 13 cases with *Pseudomonas* in the lung samples are presented in Table 11. All the infants were under 28 days of age when admitted and when the first signs of *Pseudomonas* infection became manifest, though at the time of death the oldest child was aged 5 months.

The typical presenting symptoms were the general symptoms stated in the literature: period of subnormal temperature, an indefinite poor condition, abdominal distention and omitting respiratory difficulties of various kinds, cyanosis.

TABLE 10. Relationship of mortality to *Pseudomonas* colonization and to inflammatory changes observed at autopsy in the neonatal patient during the first 3 months and the following 9 months of the present study

	Oct. 1 - Dec. 31, 1962			Jan. 1 - Sept. 30, 1963				Total	
	<i>Pseudo-</i> <i>monas</i> - colonized	Non- colonized	Total	<i>Pseudo-</i> <i>monas</i> - colonized	Non- colonized	Total	<i>Pseudo-</i> <i>monas</i> - colonized	Non- colonized	Total
Total number of neonatal patients	14	19	33	12	29	41	26	15	41
Number of deaths	9	5	14	1	11	12	13	18	31
Finding of infection at autopsy	7	2	9	1	5	6	11	5	16

-  RECOVERIES
 DEATHS WITH AUTOPSY FINDING OF INFECTION
 DEATHS WITHOUT AUTOPSY FINDING OF INFECTION
 PS+ PSEUDOMONAS COLONIZED NEONATES
 PS- NON COLONIZED NEONATES

NO. OF
NEONATES

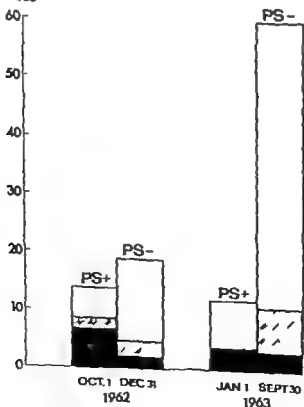


Fig. 5 Relationship of mortality to *Pseudomonas* colonization and to autopsy findings of infection in patients admitted as newborn during the first 3 months and the following 9 months of the present study

TABLE 11 *Diagnosis symptoms Pseudomonas culture and autopsy findings in Pseudomonas-coloni. 4 neonatal patients who died during the period of study*

Case No.	Sex	Basic disease	<i>Pseudomonas</i> culture findings	Symptoms	D in unit	Autopsy findings	Bacterial findings from lung
190.							
1	Female 9 hr 3,000 g	Atresia oesophagi fistula Ductus arteriosus apertus	At 5 weeks throat, nose P ₃ ++ later bronchial mucus and wound pus	Recurring pneumonia, wounds, suppurative thrombopenia cardiac insufficient	135	Bilat. pneumonia, abscesses at wound margins patent ductus arteriosus	<i>Pseudomonas</i>
2	Male 3 d. 4,060 g	Alb. Hirschsprung	At weeks throat, nose P ₃ ++ later faeces, wound pus, no discharge	Ileus, blood and mucus in faeces, wounds suppurative conjunctivitis, subnormal temperature thrombopenia	57	Pneumonia, greenish pus in abdomen, bilat. pneumonia, septicaemia	<i>Pseudomonas</i> <i>Neisseria</i>
3	Female 5 hr -650 g	Omphalocele rupture	At under 4 weeks throat P ₃ ++ later n el and faeces	Ileus, no el suppurative, subnormal temperature thrombopenia	5	Peritonitis, greenish pus in abdomen purulent bronchitis, adrenal infection	<i>Pseudomonas</i> <i>Proteus vulgaris</i>
4	Male 70 d 4,500 g	Hidradenitis P retrocephal	Culture not made	Subnormal temperature anaemic, terminal pneumonia	8	Diffuse purul parent, bilat. pneumonia	<i>Pseudomonas</i>
5	Female d 3,850 g	Atresia oesophagi fistula	On tib postoperati on bil bronchial mucus P++	Pneumonia, subnormal temperature	10	Bilat. diffuse pneumonia, right pleuritis, ruptured aerostomosis	<i>Pseudomonas</i>
6	Male 36 hr 1,870 g	Atresia duodeni Præmaturitas	Throat and nose P ₃ -	On 3rd postoperati on subnormal tem perature icterus, abdomen hard, blood and mucus in faeces	5	Pneumonitis, ulcerations in oesophageal mucosa membrane, partial pulmonary infarctus	<i>Pseudomonas</i>
	Female d 3,400 g	Atresia oesophagi Anus ect bil n Aplasia polli cris ds	Throat P++ on admission	On admission lung changes, condition poor subnormal temperature icterus, distended abdomen	4	Diffuse haemorrhages in both lungs	<i>Pseudomonas</i>
8	Male 30 h 1,560 g	Atresia oesophagi at duodeni Necrotic colitis Præmaturitas	Throat and nose P ₃ -	Condition conit usual post epistaxis of proca, subnormal temperature, icterus	3	Ulcerat bil t. bronchopneumonia	<i>Pseudomonas</i>

9	1 male b. 2,320 g	1. Atresia oesophagi with tracheal fistula 2. Atresia oesophagi with tracheal fistula 3. Atresia oesophagi with tracheal fistula	Throat and nose 1+ 1. Throat 1+ 2. Nose 1+	used and on intubated pass aspirate specimen admission on post re admission	1	Aspirate was positive	<i>Pseudomonas</i>
10	1 female b. 1,800 g	1. Atresia oesophagi with tracheal fistula 2. Atresia oesophagi with tracheal fistula	Throat and nose 1+ 1. Throat 1+ 2. Nose 1+	On 2nd postoperative day, aspiration from trachea temporal pneumonia	1	1. 1. 1. pneumonia, right pleural ruptured anastomosis	<i>Pseudomonas</i>
11	1 female b. 2,610 g	1. Atresia oesophagi with tracheal fistula 2. Atresia oesophagi with tracheal fistula	On 11th postoperative day, bronchial intubation 1+ + + later ifrost and vomit	1. 1. 1. pneumonia, right pleural ruptured anastomosis	11	1. 1. 1. pneumonia, right pleural ruptured anastomosis	<i>Pseudomonas</i>
12	1 male b. 2,950 g	1. 1. 1. oesophagi with tracheal fistula 2. 1. 1. oesophagi with tracheal fistula	On admission throat and bronchial intubation 1+ + +	1. 1. 1. pneumonia, right pleural ruptured anastomosis	11	1. 1. 1. pneumonia, right pleural ruptured anastomosis	<i>Pseudomonas</i>
13	1 male b. 3,000 g	1. 1. 1. oesophagi with tracheal fistula 2. 1. 1. oesophagi with tracheal fistula	On 3rd postoperative day, bronchial intubation and wound pure 1+ + +	1. 1. 1. pneumonia, right pleural ruptured anastomosis	+	1. 1. 1. pneumonia, right pleural ruptured anastomosis	<i>Pseudomonas</i>

Case 1

A girl born on May 17 1962 after a normal pregnancy and uneventful delivery birthweight 3,000 g and Apgar score 7-9 was admitted at the age of 9 hours because of atresia of the oesophagus.

On admission she was in good condition and oesophago-oesophagostomy by right thoracotomy was immediately done. Her immediate postoperative condition was good and prophylaxis with

and tacks 1 spoon (22, 39, 40, 50, 72) The faeces of patients with peritonitis were loose and slimy and at some stage blood-stained. Thrombopenia was found in 3 patients in most cases the count was not made. Anaemia was present in all protracted cases. Leucocyte counts varying from high to low were seen. Three patients were unusually heavily icteric and 2 had scleroderma.

Since special attention had not been paid in the first histological examination to changes typical of *Pseudomonas* infection, the lung samples from all of the 15 *Pseudomonas*-colonized newborn infants who died were re-examined. The specimens were stained by the an Gieson and haematoxylin methods.

The following were regarded as characteristic changes in *Pseudomonas* pneumonia

A. Haemorrhagic necrosis associated with vasculitis and or thrombi in the walls of small and medium-sized pulmonary muscular arteries.

B. Necrotic granuloma with haemorrhagic margins in association with the vascular changes. In connection with the changes here described, attention was paid to the presence of histologically demonstrable bacteria and absence of inflammatory cell reaction (30-40, 52).

Specific changes of this kind were found in only 5 of the re-examined cases. The changes consisted of haemorrhagic necrosis and vasculitis an additional finding of bacteria was made in 2 cases only. These 5 patients were cases 5, 10 and 15. Their detailed case reports, as well as those of 3 other patients, cases 1, 3 and 11 are given below

TABLE 11 Diagnosis symptoms *Pseudomonas* culture and autopsy findings in *Pseudomonas*-colonized neonate patients who died during the period of study

Case No	Sex	Basic disease	<i>Pseudomonas</i> culture findings	Symptoms	Days in unit	Autopsy findings	Bacterial finding from lung
1	Female 9 hr 3,000 g	Atresia oesophagi fistula Ductus arteriosus patent	At 5 weeks tl roat, nose Pt + + + + l ter bronchial mucus and wound pus	Recurring pneumonia, wounds suppurate, thrombopenia cardiac insufficiency	155	Bilat. pn umonia, abscesses at w and margins patent ductus arteriosus	<i>Pseudomonas</i>
2	Male 5 ds 4,000 g	Mb Hirschsprung	At 5 weeks throat, nose Pt + + + + later feces, wound pus, eye discharge	Ileus, blood and mucus in faeces, wounds suppurate, conjuncti itis, subnormal temperature thrombopenia	37	Peritonitis, greenish pus in abdomen, bilat. pneumonia, septicæmia	<i>Pseudomonas</i> <i>Alkalesella</i>
3	Female 5 hr 2,650 g	Omph. locie rupture	At under 4 weeks throat Pt + + + + late na el and faeces	Ileus, na el suppurate, subnormal temperature, thrombopenia	52	Peritonitis, greenish pus in abdomen purulent bronchitis, adrenal infection	<i>Pseudomonas</i> <i>Proteus vulgaris</i>
4	Male 20 ds 4,550 g	H drocephalus Porenceph. lia	Culture not made	Subnormal temperature, anaemic terminal pn monia	8	Diffuse, partly purulent, bilat. pneumonia	<i>Pseudomonas</i>
5	Female 2 ds 3,850 g	Atresia oesophagi fistula	On 4th postoperative d y bronchial mucus p + + +	Pneumonia, subnormal temperature	10	Bilat. diffuse pneumonia, right pleuritis, ruptured anastomosis	<i>Pseudomonas</i>
6	Male 56 hr 1,870 g	Atresia duodeni Præmaturitas	Throat and nose P -	On 3rd postoperative day subnormal tem- perat. no, icterus, abdomen hard, blood and mucus in feces	5	Peritonitis, ulcerations in oesophageal mucous membrane, partial pulmonary atelectasis	<i>Pseudomonas</i>
7	Female 2 ds 5,420 g	Atresia oesophagi A in est. bilat. Aplasia pollicis ds	Throat p + on admission	On admission lung changes, cond tion poo subnormal temperat. icterus, distended abdomen	4	Diffuse haemorrhages in both lungs	<i>Pseudomonas</i>
8	Male 56 hr 1,590 g	Atresia oesophagi t duodeni Mongolismus Præmaturitas	Throat and nose Pt -	Cond tion continuously poo episodes f pnosis, subnormal temperature, icterus	5	Ulcerati bronchitis, bilat. bronchopneumoni	<i>Pseudomonas</i>

1967	10	Female 17 days 2,500 g	At via oesophagi (nd) Premortem as	Throat and nose bacterial on P—	Card non necrotic prior epinephrine apnoea pneumonia subnormal temperature	+	Agarose on pneumonia	<i>Pseudomonas</i>
11	Female 8 days 2,640 g	At via oesophagi (nd) Premortem as	Throat and nose P—	On 2nd postoperative day epinephrine, sterile, subnormal temperature pneumonia	On 2nd postoperative day epinephrine, sterile, subnormal temperature pneumonia	+	Bilateral pneumonia, right pleuritis, ruptured anastomosis	<i>Pseudomonas</i>
12	Female 17 days 2,930 g	At via oesophagi (nd) Premortem as	Throat and nose P—	On 11th postoperative day bronchial mucus P++ + later throat and nose	Heard, subnormal temperature in pneumonia	++	Bilateral bronchopneumonia and haemorrhagic necrosis ruptured patent ductus arteriosus	<i>Pseudomonas</i>
13	Male 17 days 3,000 g	At via oesophagi (nd) Premortem as	Throat and nose P—	On admission throat, nose and bronchial mucus P++ + On 3rd postoperative day bronchial mucus P++ + wound red wound pus P++ +	Immediately after operation pneumonia, fluctuating temperature cardiac insufficiency	++	Bilateral pneumonia coarctation defect and hemorrhagic pulmonary necrosis	<i>Pseudomonas</i>
					On 2nd postoperative day pneumonia, wound discharge, arteriosclerosis, epinephrine P—	+	Bilateral pneumonia, right pleuritis, ruptured anastomosis	<i>Pseudomonas</i> U identified gram-negative bacillus

and attacks of pneumonia (22, 39, 40, 55, 72). The faeces of patients with peritonitis were loose and slimy and at some stage blood-stained. Thrombopenia was found in 3 patients; in most cases the count was not made. Anaemia was present in all protracted cases. Leucocyte counts varying from high to low were seen. Three patients were unusually heavily icteric and 2 had sclerodema.

Since special attention had not been paid in the first histological examination to changes typical of *Pseudomonas* infection, the lung samples from all of the 13 *Pseudomonas*-colonized newborn infants who died were re-examined. The specimens were stained by the an Gieson and haematoxylin methods.

The following were regarded as characteristic changes in *Pseudomonas* pneumonia

A. Haemorrhagic necroses associated with vasculitis and/or thrombi in the walls of small and medium-sized pulmonary muscular arteries.

B. Necrotic granulomata with haemorrhagic margins in association with the vascular changes. In connection with the changes here described, attention was paid to the presence of histologically demonstrable bacteria and absence of inflammatory cell reaction (39, 40, 52).

Specific changes of this kind were found in only 3 of the re-examined cases. The changes consisted of haemorrhagic necroses and vasculitis; an additional finding of bacteria was made in 2 cases only. These 3 patients were cases 5, 10 and 13. Their detailed case reports, as well as those of 3 other patients, cases 1, 3 and 11 are given below.

Case 1

A girl born on May 17 1962 after a normal pregnancy and uneventful delivery birthweight 3,000 g and Apgar score 7-9, was admitted at the age of 9 hours because of trauma of the oesophagus.

On admission she was in good condition and oesophago-oesophagostomy by right thoracotomy was immediately done. Her immediate postoperative condition was good and prophylaxis with

TABLE 11 *Diagnoses symptoms, Pseudomonas culture and autopsy findings in Pseudomonas colonized neonate patients who died during the period of study*

Case No	Sex	Age on admission	Birthwt.	Basic disease	<i>Pseudomonas</i> culture findings	Symptoms	Days in unit	Autopsy findings	Bacterial finding from lung
1962									
1	Female	9 h	3,000 g	Atresia oesophagi fistula	At 5 weeks throat nose P ₃ +++ later bro chial mucus and w. and pus	Recurring pneumonia, wounds suppurate, thrombopenia card ac insufficiency	155	Bilat. pneumonia, locaces t wound margins patent ductus arteriosus	<i>Pseudomonas</i>
2	M	11	4,000 g	Mb Hirschsprung	At 3 weeks throat, nose P ₃ +++ 1 ter f eces, wound pus, ey discharge	Ileus, blood and mucus in faeces, wounds suppurate, conjunctivitis, subnormal temperature, thrombopenia	57	Peritonitis, greenish pus in abdomen, bilat. pneumonia, septicaemia	<i>Pseudomonas klebsiella</i>
3	Female	5 h	2,650 g	Omph. hole	At under 4 weeks throat P ₃ +++ late na l and f eces	Ileus, na cl suppurate, subnormal temperature, thrombopenia	52	Peritonitis, greenish pus in abdomen purulent bronchitis, dorsal infection	<i>Pseudomonas Proteus vulgaris</i>
4	M	16	4,550 g	H drocephalus Porencephaly	Culture not made	S bnormal temperature, anemic, terminal pneumonia	8	D ffuse, p rly purulent, bilat. pneumonia	<i>Pseudomonas</i>
5	Female	2 d	5,830 g	Atresia oesophagi c. fistul	On 4th postoperative day bronchial mucus P+++	Pneumonia, subnormal temperature	10	Bilat. d ffuse pneumonia right pleuritis, ruptured natiomels	<i>Pseudomonas</i>
6	M	16	36 hr	Atresia duodeni Prem. teritis	Throat and nose P ₃ —	On 3rd postoperative day subnormal temperature, icterus, abdomen h rd, blood and mucus in faeces	5	Peritonitis, ulcerations in oesophageal mucous membrane, partial pulmonary atelectasis	<i>Pseudomonas</i>
7	Female	2 d	5,420 g	Atresia oesophagi An. extib. leri Aplasia pol. c. d	Throat P ₃ ++ on dissection	O dmulsion lung hangars, and fluid poo subnormal temperature icterus, distended abdomen	4	D ffuse haemorrh. ges in both lung	<i>Pseudomonas</i>
8	Male	36 h	1,500 g	Atresia oesophagi t duodeni Vag. l. anus Prem. t. ritis	Throat and nose P ₃ —	Good lion continuously poo episodic f p oca, subnormal t mperat re, icteru	3	Ule. rati bronchitis, bil t bro clasp pneumonia	<i>Pseudomonas</i>

showed anæmia and thrombopenia, with haemoglobin 9.5 g/100 ml and thrombocyte count 27,500. Treatment consisted of polymyxin in a daily dose of 2 mg/kg, gamma-globulin and, because of her clinically poor condition, cortisone. There was some improvement, but with persisting symptoms of paralytic ileus. She could not manage without cortisone, every attempt to discontinue administration being followed by rapid deterioration of her general condition. *Pseudomonas* was continuously the predominant organism from the throat, faeces and suppurating umbilicus. Polymyxin administration was followed by kanamycin and ceftazidime and there seemed to be gradual improvement. At the age of 8 weeks, when she had been almost cortisone free for days, her general condition suddenly deteriorated and she died within few hours.

Autopsy revealed foci of purulent bronchitis but in the lungs there were no signs of pneumonia or changes specific for *Pseudomonas*. This organism and *Proteus vulgaris* grew from lung samples. Abundant blue-green pus with characteristic *Pseudomonas* odour was found in the abdominal cavity. The peritoneum was dull and covered with fibrous blue-green membrane. The liver was slightly enlarged and covered with numerous fibrous membranes and adhesions of black-green-yellow colour. The medulla of the left adrenal gland was partly blue-green and microscopic examination showed a necrotising inflammation with bacteria and haemorrhagic foci.

Case 5

The patient, a girl born on October 6, 1962, at nearly 2 days old, was admitted because of oesophageal atresia. Pregnancy and delivery had been normal and her birthweight was 3,830 g and Apgar score 7.

She was in good condition on admission and oesophago-oesophagostomy by right thoracotomy was immediately performed. Moderate tenderness remained in the site of the anastomosis. Her immediate postoperative condition was good, but

daily bronchial toilettes were necessary because of profuse mucus. Prophylactically administered antibiotics were oxytetracycline, streptomycin and penicillin. Sample of bronchial mucus taken one day after operation showed no growth of bacteria, but *Pseudomonas* grew from a sample on the fourth day. At the same time there were roentgenological changes in the right lung, interpreted to be atelectasis and pneumonia infiltration. The child was icteric and had respiratory difficulties. Leucocyte and thrombocyte counts were not made at this stage. On the eighth postoperative day there was a sudden worsening in her general condition, with subnormal temperatures, anorexia and stupor throughout the night. A large area in the roentgenogram. On the suspicion of rupture of the anastomosis she was once more thoracotomized and gastrostomy was done. After the operation the child did not breathe spontaneously and she died at the age of nearly 12 days.

At autopsy a rupture was found in the posterior wall of the oesophagus at the site of the anastomosis. There was milk in the pleural cavity on the right side. The bronchial mucous membranes were reddish and contained bloody purulent discharge. Both lungs showed diffuse pneumonia and the right lung had an area of haemorrhagic necrosis adjacent to the pleura, with very slight inflammatory cell reaction at the margins. Bacteria were found at the margins of the necrotic area. There was septicæmia of the subpleural vessels. *Pseudomonas* grew from lung samples.

Case 10

A girl born April 8, 1963 was admitted at the age of 6 hours because of atresia of the oesophagus. The mother had had toxæmia of late pregnancy and normal delivery had taken place 10 days before the calculated term. The child weighed 1,800 g and received 10 Apgar points.

On admission her general condition was good and thoracotomy and oesophago-oesophagostomy were immediately performed. Cultures from nose

penicillin, streptomycin, chloramphenicol and tetracycline was instituted. At the age of 3 weeks there was an onset of respiratory difficulty and the first pharyngeal sample then taken gave a pure culture of *Pseudomonas*. When she was 4 weeks old pneumonia was diagnosed in the right lung and *Pseudomonas* grew from a sample of bronchial mucus. There were respiratory difficulties and subnormal temperature. Leucocyte counts were repeatedly less than 15 000 and thrombocytes were low in number. She received 2 mg/kg of polymyxin daily for eleven days. Improvement occurred during treatment and bacterial cultures became negative for *Pseudomonas*. Mild symptoms of cardiac insufficiency that had appeared at the same time disappeared with digitalization.

The child's weight gain was nevertheless not satisfactory and she was vomiting continually. Pyloromyotomy was therefore performed when she was 8 weeks old. Two days after operation a diagnosis of pneumonia of the right lung was again made and a bronchial mucus culture yielded *Pseudomonas*. Treatment was resumed with polymyxin and tetracycline, but discharge of mucus continued to be profuse and *Pseudomonas* was dominant in the nose and throat flora although the other symptoms disappeared. At the pneumonia stage there had again been cardiac insufficiency which was kept under control with digitalis. At this time the heart symptoms pointed to a patent ductus arteriosus.

At 11 weeks of age she again had pneumonia, now probably due to *Klebsiella* which was obtained as pure cultures from the throat and nose. There was leucocytosis up to 41 000. She was given a short treatment with kanamycin and gamma globulin with some improvement, but the vomiting persisted and her weight did not increase. A hiatal hernia that had been diagnosed was considered responsible for the vomiting, and when the child was 15 weeks old fundus plication, gastropexy and gastrostomy were performed. Postoperatively she again had pneumonia and cardiac insufficiency. Throat and nose cultures yielded *Pseudomonas* and *Klebsiella* and the blood picture showed leucocytosis up to 51 000.

The operation wound began to suppurate dehisced was resutured, and opened once more. *Pseudomonas* was constantly the predominant organism in the wound pus, *Klebsiella* and other gram negative bacilli being present variably. Treatment consisted of sulfa chloramphenicol, streptomycin and gamma globulin. The lung symptoms abated again and the cardiac insufficiency was kept under control with continuous digitalization but the vomiting persisted body weight did not increase and the wound continued to suppurate. The infant died at the age of 19 weeks following a febrile period of 5 days with no additional symptoms.

At autopsy the state of the oesophagus was found to be good. Small pneumonic foci were seen under the microscope in a few areas of the lung but alterations specific for *Pseudomonas* were not found. A number of abscesses were seen by microscope in the dermis at the margins of the operation wound. The heart was normal with the exception of a patent ductus arteriosus.

Case 3

This full term girl born after a normal pregnancy on September 23, 1962, had a ruptured omphalocele. Her birthweight was 2,650 g and Apgar score 9-10 and the delivery had been normal.

She was admitted 5 hours after birth in good condition but had a mass of intestinal loops beside the navel. At an immediately undertaken operation the intestine was repositioned but considerable tears of the muscles remained.

Her general condition was good after the operation and she received tetracycline chloramphenicol and streptomycin as prophylaxis. Intestinal passage was still poor apparently due to peritonitis, and she received continually part of her food parentally. When the child was nearly 4 weeks of age a dramatic deterioration occurred in her condition, with cyanosis, subnormal temperature and abdominal distention. The throat sample yielded a pure growth of *Pseudomonas*. The blood picture

for the pleural suction tube began to suppurate and *Pseudomonas* and a gram-negative bacillus of the *klebsiella* group grew from the pus. On the fourth postoperative day the child was very poor, septicemic and had intermittent periods of apnea. He died 4 1/2 days after operation. The thrombocytes had not been examined the leucocyte count on the day of death was 8,800. Penicillin and streptomycin had been administered as prophylactic antibiotic treatment throughout the time of hospitalization.

At autopsy the oesophageal anastomosis was found to be partially opened and there was pus in the adjacent part of the mediastinum. The pleura on the right side had a fibrinous covering, the air content was reduced in both lungs and pus oozed from the lung tissue on compression. There also was pus in the bronchi. Histological examination showed in both lungs pneumonic changes and a number of foci of haemorrhagic necrosis, and in the small arteries partially obstructing scleritis. At the margins of the necrotic areas there were bacteria but only slight inflammatory cell reaction. Lung sample cultures yielded *Pseudomonas* and an unidentified gram-negative rod bacillus.

Neonates with Oesophageal Atresia. Among the 76 *Pseudomonas*-colonized newborn infants the largest uniform group was comprised of the 15 patients with atresia of the oesophagus and one patient with trachio-oesophageal fistula (Table 8). Nearly two-thirds of the 24 patients treated in the unit for oesophageal atresia during the period of this study were *Pseudomonas*-colonized.

Mortality in the group of 24 neonates with oesophageal atresia during the period was 15 patients, or over half of these patients (Table 12). Nine of those who died were *Pseudomonas*-colonized. At autopsy pneumonia was confirmed in 7 of the latter whereas it was present in only one of the 4 non-colonized infants with oesophageal atresia who died.

In Table 12 the patients with oesophageal atresia are distributed into groups that have significance from the point of prognosis (56, 171). The correlations between these groups and *Pseudomonas* colonization, mortality and autopsy finding of pneumonia are presented.

Twelve of the newborn patients who on admission were in good general condition graded as A died 10 and 4 day after operation in both cases *pseudomonas* pneumonia was diagnosed during

TABLE 12 Condition on admission of neonates with oesophageal atresia and relationship to *Pseudomonas* colonization, mortality and autopsy finding of pneumonia.

	<i>Pseudomonas</i> -colonized			Non-colonized			Total		
	No. of cases	No. of deaths	<i>Pseudomonas</i>	No. of cases	No. of deaths	<i>Pseudomonas</i>	No. of cases	No. of deaths	<i>Pseudomonas</i>
Group A Birth weight over 2.5 kg good condition	4	2	2	5	0	0	9	2	2
Group B Birth weight 1.5-2.5 kg good condition or higher birth weight but child had also other anomalies or pneumonia	7	4	3	5	2	1	10	6	4
Group C Birth weight under 1.5 kg or higher but child had severe pneumonia or gross anomaly	3	3	2	2	2	0	5	5	2
Total number of patients with oesophageal atresia	14	9	7	10	4	1	24	15	10

and throat samples taken on admission were negative. Postoperative recovery was at first uneventful penicillin and streptomycin were given as prophylactic medication. Two days after operation her temperature fell suddenly to below 31°C and she became icteric and scleroedemic. Roentgenograms revealed slight changes in the right lung. Blood examinations were not made at this time. Cortisone was administered for the scleroedema. On the following day there were clear signs of rupture of the oesophageal anastomosis, pleural suction brought out food, and there were extensive roentgenological changes in the right lung. Gastrostomy was done on the same day following which the child died at the age of slightly over 4 days.

At autopsy the oesophageal anastomosis was found to have opened completely. The surface of the right lung was covered with a green fibrinous coating. Histologically both lungs exhibited haemorrhagic areas and some haemorrhagic necrotic foci with diffuse margins, associated with obstructive vasculitis. No bacteria were found. The necrotic areas showed hardly any inflammatory cell reaction. Bacterial cultures of lung samples yielded *Pseudomonas*.

Case 11

A girl born on August 15 1963 after a normal pregnancy was admitted at the age of 2 days because of atresia of the oesophagus. Delivery had been normal and her birthweight had been 2,640 g and Apgar score 10.

The condition of the child was good on admission and oesophago-oesophagostomy through right thoracotomy was immediately performed.

Following the operation the child suffered from very profuse mucus in her airways and constant bronchial toilettes were necessary. Antibiotic prophylaxis consisted of penicillin and streptomycin. When she was 5 days old, gastrostomy was done because of vomiting. One day later roentgenograms showed mild pneumonic changes in both lungs, and *Pseudomonas* grew in cultures of bronchial mucus. She had respira-

tory difficulties, a subnormal temperature and icterus. The haemoglobin, leucocyte and thrombocyte levels were normal. Feeding by gastrostomy tube was not successful, the child continually vomited and laparotomy was therefore done when she was 8 days old on the suspicion of pyloric stenosis. No obstruction to intestinal passage was found. The medication was supplemented with chlaramphenicol. Her condition continued to deteriorate and the vomiting and abdominal distention persisted. When the child was 11 days old there were extensive roentgenological changes in the right lung and she died at the age of 12 days.

Autopsy revealed at the site of the anastomosis in the oesophagus a small rupture opening into the right pleural cavity. The trachea contained blood-stained purulent exudate. Haemorrhagic areas were present in both lungs beneath the pleura. Fibrinous adhesions were seen on the pleural surface on the right. Histological examination of lung tissue showed numerous collapsed areas, and there were some leucocytes and haemorrhages here and there in the bronchi and alveoli. Changes specific for *Pseudomonas* infection were not found. Lung sample cultures showed growth of *Pseudomonas*. An additional finding was a patent ductus arteriosus.

Case 12

This patient was a boy born on September 6 1963 after a normal pregnancy. Birthweight was 3,000 g and the Apgar score 9-10. He was 1 day old when admitted because of atresia of the oesophagus.

On admission he was in a good condition and oesophago-oesophagostomy through right thoracotomy was performed at once. Samples of nose, throat and bronchial mucus taken at the time of admission were negative for *Pseudomonas*.

His immediate postoperative state was good, but 2 days later rales were audible over the lungs and he had respiratory difficulties. Sample of bronchial mucus taken 3 days after operation gave pure culture of *Pseudomonas*. The opening

for the pleural suction tube began to suppurate and *Pseudomonas* and a gram-negative bacillus of the *Klebsiella* group grew from the pus. On the fourth postoperative day the child was very poor sclerodemous and had intermittent periods of prostration $\pm 1/2$ days after operation. The thrombocytes had not been examined the leucocyte count on the day of death was 8,800. Penicillin and streptomycin had been administered as prophylactic antibiotic treatment, throughout the course of hospitalization.

At autopsy the oesophageal anastomosis was found to have partially opened and there was pus in the adjacent part of the mediastinum. The pleura on the right side had fibrinous covering, the air content was reduced in both lungs and pus oozed from the lung tissue on compression. There also was pus in the bronchi. Histological examination showed in both lungs pneumonic changes and a number of foci of haemorrhagic necrosis and in the small arteries partially obstructing acutitis. At the margins of the anastomosis there were bacteria but only slight inflammatory cell reaction. Lung sample cultures yielded *Pseudomonas* and an unidentified gram negative rod bacillus.

Neonates with Oesophageal Atresia. Among the 26 *Pseudomonas*-colonized newborn infants the largest uniform group was comprised of the 13 patients with atresia of the oesophagus and one patient with tracheo-oesophageal fistula (Table 8). Nearly two-thirds of the 24 patients treated in the unit for oesophageal atresia during the period of this study were *Pseudomonas*-colonized.

Most likely in the group of 24 neonates with oesophageal atresia during the period was 15 patients, or one half of these patients (Table 12). Nine of those who died were *Pseudomonas*-colonized. At autopsy pneumonia was confirmed in 7 of the latter whereas it was present in only one of the 4 non-colonized infants with oesophageal atresia who died.

In Table 12 the patients with oesophageal atresia are distributed into groups that have significance from the point of prognosis (38, 171). The correlations between these groups and *Pseudomonas* colonization, mortality and autopsy finding of pneumonia are presented.

Two of the newborn patients who on admission were in good general condition graded as A died 10 and 4 days after operation in both cases pseudomonal pneumonia was diagnosed during

TABLE 12 Condition on admission of neonates with oesophageal atresia and relationship to *Pseudomonas* colonization, mortality and autopsy finding of pneumonia.

	<i>Pseudomonas</i> -colonized			Non-colonized			Total		
	No. of cases	No. of deaths	Pneumonia	No. of cases	No. of deaths	Pneumonia	No. of cases	No. of deaths	Pneumonia
Group A Birthweight over 2.5 kg. good condition	4	2	2	5	0	0	9	2	2
Group B Birthweight 1.8-2.5 kg. good condition, or higher birthweight but child had also other anomalies or pneumonia	7	4	3	3	2	1	10	6	4
Group C Birthweight under 1.8 kg. or higher but child had severe pneumonia or gross anomaly	3	3	2	2	2	0	5	5	0
Total number of patients with oesophageal atresia	14	9	7	10	4	1	24	15	8

life (Table 11 cases 5 and 13) The immediate cause of death of these two patients was rupture of the anastomosis.

In group B 6 newborn infants died, 1 of whom were *Pseudomonas*-colonized (Table 11 cases 1, 7, 10 and 11) *Pseudomonas* pneumonia had been diagnosed already during life in 2 cases and it was diagnosed at autopsy in a further case. In 2 of these cases the immediate cause of death was rupture of the anastomosis.

All the infants in group C died. Three were *Pseudomonas*-colonized and 2 of these had pneumonia which was observed during life in one case (Table 11 No. 12) but not before autopsy in the other case (No. 8).

Among the non-colonized 10 patients operated on for oesophageal atresia the anastomosis was found to be ruptured in one case only. This patient had no signs of infection.

All the *Pseudomonas*-colonized infants in group A who recovered had been free from symptoms, while in group B one infant had had pneumonia and one conjunctivitis.

Various bacterial infections in the newborn. One or more bacterial infections were found in 16 (41%) of the 104 newborn infants under

treatment in the unit during the period studied (Table 13). The largest number of infections were caused by gram negative bacilli, i.e. six times as many as by *Staphylococci*. Over a third of the bacillary infections were due to *Pseudomonas*, the following in frequency being those due to bacilli of the *Klebsiella* group and to *E. coli*. Infections caused by various other gram negative bacilli as those of the *Proteus* and *Alcaligenes* *Dispar* groups, *Alcaligenes* *faecalis* and others, formed a group of nearly the same size as that due to *Pseudomonas* alone.

Among the newborn infants, carriers of the three most important pathogenic organisms, *Pseudomonas*, *Klebsiella* and *Staphylococcus*, were about equal in number (Table 13). Nevertheless, the infections that developed during their stay in hospital were six times as often caused by *Pseudomonas* and *Klebsiella* as by *Staphylococcus*. A finding of *Pseudomonas* at autopsy was remarkably more often associated with histological signs of infection than a finding of other bacteria (Table 13). The differences were statistically almost significant.

Antibiotic and gamma globulin treatment of the newborn. During the period studied, anti-

TABLE 13 Species of bacteria isolated from the neonate patients: number of infections caused by them, time of diagnosis of infection, and relationship to autopsy findings of infection

Bacterial	Colonized neonates	Infected bacterium	Symptoms admission	Symptoms later	No. of deaths among colonized neonates	Autopsy findings of positive culture from lung and histological infection
<i>Pseudomonas</i>	26	1	3	14	14	11**
<i>Klebsiella</i>	28	12		10	10	2*
<i>Escherichia coli</i>	21	10	9	1	1	1
Other gram negative bacilli	39	16	7	9	3	2**
<i>Staphylococcus aureus</i>	23	9	5	4	4	2
<i>Streptococcus faecalis</i>	14	9	1	2	2	0
Other bacterial cultures	11	0	1	0	0	3

) Both *Pseudomonas* and *Klebsiella* grew in the culture in question.

**) Both *Pseudomonas* and *Proteus vulgaris* grew in the culture in question.

biotics were used very extensively for prophylaxis. The commonly used combination was penicillin and streptomycin, with additionally chloramphenicol or some drug of the tetracycline group. During the first 3 months of the period, three or more antibiotics were administered to over a third of the infants admitted as newborn, and in the following 9 months to only a fifth of the neonates (Table 14). About half of the 104 hospitalized newborn received two antibiotics and only less than fourth had no antibiotic therapy. With one exception, all the *Pseudomonas*-colonized infants had received two or more antibiotics during at least 3 days before colonization was diagnosed. Statistically analysed there were almost significantly more *Pseudomonas*-colonized newborn infants in the group given antibiotics than in the group not administered these drugs.

During the first 3 months of the studied period 4 patients received polymyxin for the treatment of *Pseudomonas* infection. Colistin was given to 8 neonates, i.e. in 2 cases for treatment after finding of *Pseudomonas* colonization and in 6 cases for prophylaxis. One of the latter became colonized. All the patients who were given colistin were with one exception, under treatment during the last 2 months of the period studied.

Gamma-globulin was administered during the first 3 months to 4 neonate patients for treatment of diagnosed *Pseudomonas* infection. In the following 9 months 7 infants received gamma-globulin; in 6 cases it was administered for

prophylaxis and one of these infants became colonized.

B Urological Patients

At same stage, *Pseudomonas* bacilli were isolated from the urine of 8 of the 22 urological patients treated in the paediatric surgical unit (Table 8). In 4 of these cases there was a positive finding in the urine on admission; 4 infants became colonized during hospitalization in the unit. Those found to be colonized on admission had been treated in the same unit 1-3 months earlier, and that these *Pseudomonas* had appeared into the urine. In also these cases the contamination was possibly acquired in the unit. There were no cases of death among either *Pseudomonas*-colonized or non-colonized urological patients.

All the children found to have become colonized while in the unit had undergone an operation of the urinary tract 4-14 days before the finding of *Pseudomonas* in the urine and postoperatively they had had an indwelling catheter or other urinary tract drain during 4-10 days.

Pseudomonas was the only organism found in the urine of 4 patients, all of whom had definite pyuria and localized suppurating processes at the site of insertion of the drain. Body temperature was over 38 °C in one case only. The bacteruria and pyuria persisted in these cases during the remaining 10-24 days of their stay in the hospital.

TABLE 14. Treatment of the neonate patients with antibiotics and relationship to *Pseudomonas* colonization during the first 3 months and the following 9 months of the present study

Number of antibiotics administered	Oct 1 - Dec. 31 1962		Jan. 1 - Sept. 30, 1963		Total	
	No. of cases	No. of <i>Pseudomonas</i> -colonized	No. of cases	No. of <i>Pseudomonas</i> -colonized	No. of cases	No. of <i>Pseudomonas</i> -colonized
3 or more antibiotics	15	8	14	4	27	12
2 antibiotics	16	6	38	7	54	13
1 antibiotic	0	0	1	0	1	0
No antibiotic	4	0	11	1	15	1
Total number of neonate patients	35	14	71	12	104	26

* Colistin given as the other antibiotic to 6 infants.

lifo (Table 11 cases 5 and 13) The immediate cause of death of these two patients was rupture of the anastomosis.

In group B 6 newborn infants died, 4 of whom were *Pseudomonas*-colonized (Table 11 cases 1 7 10 and 11) *Pseudomonas* pneumonia had been diagnosed already during life in 2 cases and it was diagnosed at autopsy in a further case In 2 of these cases the immediate cause of death was rupture of the anastomosis.

All the infants in group C died Three were *Pseudomonas*-colonized and 2 of these had pneumonia, which was observed during life in one case (Table 11 No 12) but not before autopsy in the other case (No. 8)

Among the non-colonized 10 patients operated on for oesophageal atresia the anastomosis was found to be ruptured in one case only This patient had no signs of infection.

All the *Pseudomonas*-colonized infants in group A who recovered had been free from symptoms, while in group B one infant had had pneumonia and one conjunctivitis.

Various bacterial infections in the newborn One or more bacterial infections were found in 46 (41%) of the 104 newborn infants under

treatment in the unit during the period studied (Table 13) The largest number of infections were caused by gram negative bacilli i.e., six times as many as by *Staphylococcus*. Over a third of the bacillary infections were due to *Pseudomonas*, the following in frequency being those due to bacilli of the *Klebsiella* group and to *E. coli* Infections caused by various other gram negative bacilli as those of the *Proteus* and *Alcaligenes* *Dispar* groups, *Alkaligenes faecalis* and others, formed a group of nearly the same size as that due to *Pseudomonas* alone

Among the newborn infants, carriers of the three most important pathogenic organisms, *Pseudomonas*, *Klebsiella* and *Staphylococcus* were about equal in number (Table 13) Nevertheless, the infections that developed during their stay in hospital were six times as often caused by *Pseudomonas* and *Klebsiella* as by *Staphylococcus*. A finding of *Pseudomonas* at autopsy was remarkably more often associated with histological signs of infection than a finding of other bacteria (Table 13) The differences were statistically almost significant.

Antibiotic and gamma-globulin treatment of the newborn During the period studied, anti

TABLE 13 Species of bacteria isolated from the neonate patients number of infections caused by them time of diagnosis of infection, and relationship to autopsy findings of infection

Bacterium	Colonized neonates	Infection due to the bacterium	Symptoms on admission	Symptoms according to	No. of death among colonized neonates	Autopsy findings of positive culture from lung and histological infection
<i>Pseudomonas</i>	26	17	5	14	13	11**
<i>Klebsiella</i>	28	12	2	10	10	2*
<i>Escherichia coli</i>	30	10	9	1	1	1
Other gram-negative bacilli	39	16	7	9	9	7*
<i>Staphylococcus aureus</i>	25	9	5	1	1	2
<i>Streptococcus faecalis</i>	14	9	1	2	2	1
Other bacterial cultures negative	14	0	0	0	0	0

* Both *Pseudomonas* and *Klebsiella* grow in the culture.
 ** Both *Pseudomonas* and *Klebsiella* grow in the culture.

examination of the lungs showed extensive intra-alveolar and intrabronchial haemorrhages and necrotic areas, many haemorrhagic necrotic foci, and in the small arteries partially occluding acutely. Inflammatory cell reaction was light around the necrotic areas. No bacteria were seen. Growth of *Pseudomonas* was obtained in cultures of samples from the lungs.

The heart had high endocardial septal defect and tricus arteriosus communis.

Case B

A girl born on February 27 1963, birthweight 2690 g, had been hospitalized in this unit for the first time from February 27 to April 30 1963 because of duodenal atresia and hydrocephalus. Reticulic duodeno-jejunostomy was done when she was one day old. Postoperatively recovery was good, but when the child was 3 weeks old myeloid meso-peritoneostomy was performed because of the rapidly progressing hydrocephalus. During her stay in the surgical unit nose sample showed slight growth of *Pseudomonas* when she was 3 weeks old, but later samples were negative. Antibiotic prophylaxis was penicillin and streptomycin. When 1 1/2 months of age she was transferred to another hospital for observation.

She was re-admitted to the unit under study at the age of 7 months because of the progressive growth of the head. On admission the circumference of the head was 59 cm and her general condition was poor. The cerebrospinal fluid

showed no inflammatory changes. *Pseudomonas* did not grow from nose and throat samples. On the day after re-admission a Spitz Hoffer extraculo-jugulotomy was done. On the fifth post-operative day her temperature rose to 38.5 C and she was vomiting the cerebrospinal fluid contained 260 leucocytes per mm³ and large numbers of gram-negative bacilli, and culture yielded *Pseudomonas*. During her present stay in the unit she received no antibiotic prophylaxis. penicillin treatment was instituted after the meningitis had been diagnosed. The child's condition became progressively poorer, the febrile temperature fell, haemoglobin dropped to 6 g/100 ml and she died 17 days after operation.

Autopsy showed enormous cerebral ventricles. There was pus on the inner surface of the ventricles and on macroscopic examination a thick layer of pus was seen on the meninges. Both lungs showed massive purulent pneumonia and circumscribed haemorrhagic necrotic foci, in the centre or margin of which there was marked destruction of the walls of the small and medium-sized arteries by vasculitis. The right lung had a large haemorrhagic necrotic area about 5 mm in diameter and the adjacent medium-sized pulmonary artery showed necrotic vasculitis and obstructive thrombus. Adjacent to the necrotic area last mentioned there were histologically demonstrable bacteria. Foci of infection were also seen in the left heart and kidneys. Growth of *Pseudomonas* and *E. coli* was obtained in cultures of samples from the lungs.

Klebsiella was a finding concomitant with *Pseudomonas* in the urine of 4 patients. In these cases the *Klebsiella* probably had more significance, since *Pseudomonas* occurred only from time to time in the urine samples of these patients.

Bacteruria developed in 10 of the 22 urological patients during hospitalization. Bacterial cultures from urine yielded *Pseudomonas* alone in one case only, *Escherichia coli* and *Klebsiella* in 3 cases, *Klebsiella* in 5 cases, and *E. coli* likewise in 5 cases.

C Other Patients

Apart from the patients who were admitted to the paediatric surgical unit as newborn or as urological cases, a total of 37 children under 2 years were treated in the unit during the 12 month period studied (Table 5). Nineteen (51%) of the latter were found to be *Pseudomonas* colonized. The finding was made on admission in 12 cases, or in 63% of the patients. Seven children or about 20% of this group became colonized later.

The greater part of the *Pseudomonas*-colonized children in this group were asymptomatic carriers of the organism in the nose and throat totalling 12. Nine of these were *Pseudomonas*-colonized when admitted.

Symptoms of infection caused by *Pseudomonas* were seen in 7 children (18% of the group). A urinary tract infection due to this organism developed in 2 children who had an indwelling catheter: a patient operated on for hydrocephalus had pseudomonas meningitis, and in one patient there developed a mixed infection with *Pseudomonas* and *Staphylococcus aureus* in the tracheal cannula wound. Already on admission 2 children had conjunctivitis and tit and one patient had pneumonia all caused by *Pseudomonas*.

In this group of 37 children there were 21 deaths. Four of those who died were *Pseudomonas*-colonized. In one case culture from the lung made at autopsy was positive for *Pseudomonas* but this was not significant of an infection. A third patient had had a mild wound infection

during life but at autopsy the lung culture and microscopic examination were negative for *Pseudomonas* and infection. Two children had during life had clearly a *Pseudomonas* infection, which was meningitis and septicaemia in one case and pneumonia in the other. In both cases the histological examination at autopsy revealed changes in the lungs typical of *Pseudomonas* infection. These patients are presented below.

Case 1

This patient was a girl born on July 13, 1963. Birthweight was 3700 g and the Apgar score 9. Immediately after delivery a heart murmur was audible but the child progressed quite well during the first 4 weeks. At this time there was onset of respiratory difficulties and cyanosis, and when 6 weeks of age she was sent by the local hospital to the Children's Hospital of the Helsinki University Central Hospital.

The child was first admitted to the paediatric unit. Examination on admission showed a poor general condition, cyanosis, profuse mucus in the airways, systolic and diastolic heart murmur and enlargement of the liver to 5 cm below the costal arch. Body weight was 4250 g. There was fever up to 38°C. Radiological findings were an enlarged heart and diffuse pneumonia in the right lower lobe. Samples were not taken for bacterial culture. Haemoglobin was 11.6 g/100 ml, leucocyte count 28,000 and thrombocyte count normal. Intravenous erythromycin and ampicillin treatment and digitalization were instituted. Two days later she was transferred to the paediatric surgical unit because of the respiratory difficulty and ventilated on a respirator. Nose and throat samples were taken on admission to the unit and yielded pure cultures of *Pseudomonas*. At the time the child's temperature was abnormal discharge of mucus continued to be copious and she could not tolerate oral fluid. Respirator Haemoglobin fell to 10.4 g/100 ml. The child died 14 days after admission to the surgical unit.

At autopsy revealed blood in the trachea and numerous hemorrhagic areas beneath the pleura and in the interlobular fat of the lungs. Histological

The later cases of colonization during hospitalization occurred after *Pseudomonas*-colonized children with manifest infection had arrived in the unit. These may have been entirely separate epidemics.

Type of patients. It has been demonstrated that a hospital epidemic due to *Pseudomonas* arose readily when the type I patients susceptible to infection came into contact with heavy disseminators of the infective organism (9, 167). All the patients in the unit under study were susceptible because of their age, limited proportion of them had received large amounts of antibiotics for prophylaxis, and throughout the studied period part of the patients were premature or full-term neonates with various congenital anomalies who had undergone major operations, i.e., patients of the type found to be particularly susceptible to infection with *Pseudomonas* (13, 23, 28, 72, 79, 180, 175, 180).

Urology disseminators of *Pseudomonas* bacilli can be regarded especially the infected urological patients (106, 150, 164) and the patients with various forms of superficial purulent *Pseudomonas* infections or with pneumonia. A relatively large number of such patients were being treated in the unit especially at the beginning and end of the studied period.

Hygiene in the unit. During the first few months of the period studied no systematic efforts were made to prevent the spreading of *Pseudomonas* bacilli. The *Pseudomonas*-colonized children were treated with the non-colonized ones in the ward and the operating theatre with no isolation measures of any kind being taken. Hexachlorophene and benzalkonium chloride substances that are poorly effective against *Pseudomonas* were used for the disinfection of the hands, equipment and environment.

After the first 3 months of the period the children found to be *Pseudomonas*-colonized were systematically isolated, and greater emphasis was placed on hand hygiene and on the cleansing and sterilization of equipment and utensils. However, no change was made in the disinfectants used.

Relative importance of the different factors. It is seen from the foregoing that during the first 3 months of this study there existed all the preconditions for continuation of the earlier epidemic. The definite decrease in the number of cases thereafter may possibly be ascribed to a number of causes. Among these reasons were most probably the removal from the unit of at least the transmitters of massive contagion and the destruction of foci of infection in the equipment through more efficient control and cleansing.

Twice late *Pseudomonas* was again found to have spread among the patients in the unit probably following the admission of heavily *Pseudomonas*-infected patients. These patients were in poor condition on arrival and they needed much attention and handling; furthermore the presence of the *Pseudomonas* infection was not known in all cases on admission and this facilitated spreading of the organism. Very probably the ceasing of the epidemic at both times (the last epidemic did not continue beyond the period of this study) was to a marked extent brought about by improved hygiene in the unit and possibly also by alterations in antibiotic prophylaxis.

Possible Routes of Transmission of *Pseudomonas*

Transmission by hands. A number of patients who may be considered to have caused heavy contamination of the hands of the nursing staff were hospitalized in the unit during the investigated period, particularly at the various times when spreading of *Pseudomonas* was noted. Such probable contaminators were urological patients with *Pseudomonas* infection, patients with suppurating wounds, and patients with severe pneumonia and a copious *Pseudomonas* flora in the discharge from the throat and trachea. Many of these infants were in poor condition and required much handling, and the numerous emergency situations that occurred allowed no time for precautionary measures.

Discussion

Nature of Occurrence of *Pseudomonas*

Pseudomonas bacilli were isolated from a rather large proportion, 10 %, of patients treated in the paediatric surgical unit during the 12 month period of study. Since a systematic search was not made for faecal and skin carriers, the number of carriers was presumably still greater (22, 18-116). According to the literature, the frequency incidence of *Pseudomonas* colonization among the non hospital population of the same age is in general lower and therefore the incidences obtained in this study points to contamination acquired in the hospital environment.

Half of the *Pseudomonas* carriers found were colonized already at the time of admission to the unit; earlier hospital contacts should presumably be regarded as the sources of the bacillus in these cases. Whereas the children found to be colonized on admission were fairly evenly distributed over the period studied, the figures for those colonized while in the unit were highest in October-December 1962, March-April 1963 and August-September 1963. Into these periods were also centred most of the diagnosed *Pseudomonas* infections. *Pseudomonas* positive cultures from lung samples at autopsy and the heaviest environmental contamination in the unit.

The patients who died particularly in this unit gave *Pseudomonas* positive cultures from lung samples at autopsy in a very high incidence of cases. This incidence was of the same order of magnitude as that reported earlier in the literature (152) and differed statistically significantly from the incidence among infants dying during the same period in the prematures ward and

the infection ward for children under 2 years of age.

Since facilities for the typing of *Pseudomonas* strains were not yet available at the time the present study was made, definite conclusions can not be drawn concerning the source and mode of transmission of the strains found in the patients and in the unit environment. However in the light of the results presented it appears probable that conditions in the paediatric surgical ward and operation unit were favourable for the spreading of *Pseudomonas* bacilli and infections, especially during the first three and last two months of the period studied.

Factors Promoting Outbreak of the Epidemics

Source of Pseudomonas The observation has been reported in the literature that one and the same *Pseudomonas* type may give rise to infections in the same hospital unit in the course of many weeks and even of months (167). In the paediatric surgical unit studied in the present investigation there had occurred numerous cases of *Pseudomonas* infection during the months preceding the commencement of the investigation in October 1962, and some cases had been observed already in 1961 (152). A part of the *Pseudomonas*-colonized patients under treatment in the unit in the early part of the studied period had had the infection already before the study was begun, and it is therefore very probable that the numerous cases of *Pseudomonas* infection during the first months of study were a continuation of an earlier pandemic.

The later cases of colonization during hospitalization occurred after *Pseudomonas*-colonized children with manifest infection had arrived in the unit. These may have been entirely separate epidemics.

Type of patients. It has been demonstrated that hospital epidemic due to *Pseudomonas* arises readily when the type of patients susceptible to infections come into contact with heavy disseminators of the infective organism (99, 167). All the patients in the unit under study were susceptible because of their age, marked proportion of them had received large amounts of antibiotics for prophylaxis, and throughout the studied period part of the patients were premature or full-term neonates with anoxic congenital anomalies who had undergone major operations, i.e. patients of the type found to be particularly susceptible to infection with *Pseudomonas* (15, 23, 36, 72, 79, 160, 175, 180).

As heavy disseminators of *Pseudomonas* bacilli can be regarded especially the infected urological patients (106, 150, 164) and the patients with anoxic forms of superficial purulent *Pseudomonas* infections or with pneumonia. A relatively large number of such patients were being treated in the unit especially at the beginning and end of the studied period.

Hygiene in the unit. During the first few months of the period studied no systematic efforts were made to prevent the spreading of *Pseudomonas* bacilli. The *Pseudomonas*-colonized children were treated with the non-colonized ones in the ward and the operating theatre with no isolation measures of any kind being taken. If *hexachlorophene* and *benzalkonium chloride* substitutes that are poorly effective against *Pseudomonas*, were used for the disinfection of the hands, equipment and environment.

After the first 3 months of the period the children found to be *Pseudomonas*-colonized were systematically isolated, and greater emphasis was placed on hand hygiene and on the cleansing and sterilization of equipment and utensils. However no change was made in the disinfectants used.

Relative importance of the different factors.

It is seen from the foregoing that during the first 3 months of this study there existed all the preconditions for continuation of the earlier epidemic. The definite decrease in the number of cases thereafter may possibly be ascribed to a number of causes. Among these reasons were most probably the removal from the unit of at least the transmitters of mass contagion and the destruction of foci of infection in the equipment through more efficient control and cleansing.

Twice later *Pseudomonas* was again found to have spread among the patients in the unit probably following the admission of heavily *Pseudomonas*-infected patients. These patients were in poor condition on arrival and they needed much attention and handling; furthermore, the presence of the *Pseudomonas* infection was not known in all cases on admission and this facilitated spreading of the organism. Very probably the ceasing of the epidemic at both times (the last epidemic did not continue beyond the period of this study) was to a marked extent brought about by improved hygiene in the unit and possibly also by alterations in antibiotic prophylaxis.

Possible Routes of Transmission of Pseudomonas

Transmission by hands. A number of patients who may be considered to have caused heavy contamination of the hands of the nursing staff were hospitalized in the unit during the investigated period, particularly at the various times when spreading of *Pseudomonas* was noted. Such probable contaminators were urological patients with *Pseudomonas* infection, patients with suppurating wounds, and patients with severe pneumonia and copious *Pseudomonas* flora in the discharge from the throat and trachea. Many of these infants were in a poor condition and required much handling, and the numerous emergency situations that occurred allowed no time for precautionary measures.

Although no actual evidence can be presented for the transmission of part of the infection by the hands of the staff the conclusion that the hands were contaminated can be drawn from the finding of contamination in the stationary washbasins, especially in rooms where there were *Pseudomonas*-colonized patients. Earlier studies have shown that after massive contamination with *Pseudomonas* it is difficult to fully free the hands of the organism even by meticulous washing and disinfectants (100). Furthermore hexachlorophene, which was used in cleansing of the hands at the time of the present study has a weak action against *Pseudomonas*. On these grounds it appears very probable that the handling of a massively contaminated patient led to transmission of the infective agent either to another patient or to hospital equipment.

Transmission by hospital equipment In this study *Pseudomonas* was isolated from several items of ward and operation unit equipment, instruments and furniture of kinds that very probably can transmit an infective agent.

Pseudomonas was obtained from the rubber tube and tube connector of an anaesthesia machine during the second month of this study. At that time the machines were still being used for the anaesthetization of a number of patients successively in the course of the day and were cleaned only after operations were finished for the day. Since at this time the *Pseudomonas*-colonized patients were treated in the operation room along with the other patients, it seems quite evident that the organism may have entered the respiratory tract of the following patients by this means. Transmission of infection by way of anaesthesia machines has been described in the literature possibly an anaesthetized patient is more susceptible to contract infection of the lungs (71, 152, 179, 181).

Evidence speaks for transmission by the anaesthesia equipment in the present study are the large number of lung infections and of *Pseudomonas* positive cultures from lung samples during the first months of the study period. Furthermore the organism was not found in other equipment that would have been able to convey

it into the respiratory tract, as nebulizers, oxygen equipment and respirators.

On the other hand, the organism was found in the kitchen sink and a kitchen brush and in bottles for continuous drip-feeding of newborn that were assumed to be sterile. The unit had no facilities for the sterilization of food dishes by boiling; the dishes of isolated patients were immersed for a time in a solution of benzalkonium chloride and then washed in the usual manner. The food proteins presumably reduced further the low potency of this solution and the dishes may have still been contaminated after the cleaning process.

The positive bacterial cultures obtained from the stationary washbasins are possibly of little significance in the spreading of the infection and may be considered only a sign of contamination of the hands in the ward and operation unit. The bacillus was not found in samples taken from the mouth of the water tap which would have suggested contamination of the water but only from the mouth of the washbasin drain.

Infection with *Pseudomonas* has been observed to spread from patient to patient in connection with bathing (165). The organism was found in bathtub drains at only about the middle and end of the studied period and even in those cases in the bathtubs of rooms where *Pseudomonas*-colonized patients were isolated. Bathtubs may possibly have been one of the routes of transmission in the early period when the colonized patients were housed among the non-colonized even if the cultures of samples from the bathtubs were negative for *Pseudomonas*.

Most of the newborn were postoperatively placed in incubators. Only one finding of *Pseudomonas* was made in this type of equipment and this particular incubator was thoroughly cleaned until repeated bacterial cultures were negative. Transmission of the infective agent by this route therefore seems unlikely.

In the sluice room, infection may naturally have spread from heavily contaminated brushes to the utensils being cleaned and to the hands of the personnel and thus back into the ward to other patients.

The possibility cannot be excluded that infection may have been transmitted also by means of items of equipment which were not examined for *Pseudomonas* or which at the time of examination were uncontaminated.

Since facilities were not available for typing of the *Pseudomonas* strains found in the equipment used in the unit it is not possible to conclude whether or not these strains were identical with those that caused symptoms of infection in the patients. In any case it can be said that the contamination of hospital equipment constituted a marked infection hazard to the patients.

Transmission by air and dust. Especially in the case of epidemic respiratory tract infections caused by *Pseudomonas*, transmission by air has been considered (described) important route in the spreading of the infection. Since during the period studied, *Pseudomonas* was not found either on the settling plates or in floor dust, transmission by this route appears to have been of minor significance.

Transmission by the hospital staff. Since no nasal or throat carriers of *Pseudomonas* were found in either the ward or the operation unit staff transmission in this manner seems unlikely. However the staff was not examined for faecal carriers and there might have been members of the personnel who were carriers of an epidemic *Pseudomonas* strain. Earlier studies have shown however that faecal carriers of *Pseudomonas* in hospital staff are generally very few in number and of minor significance in the transmission of the infection agent (18, 22, 99).

Occurrence and Significance of *Pseudomonas* Infections

Although all the patients treated in the paediatric surgical unit for children under 2 years of age can be considered to be susceptible to *Pseudomonas* infection (81), the *Pseudomonas*-colonized patients and those who developed symptoms of the infection were mostly found among the neonate and urological patients. In

addition to the clearly demonstrated susceptibility of these groups to infections with gram-negative bacilli of all kinds, a number of other factors may have contributed to the high incidences in these two groups of patients.

These were patients who were being most closely observed and from whom samples were frequently taken for bacterial culture. In the other groups there were occasionally large numbers of patients in good condition whose stay in the hospital lasted only a few days and from whom samples for culture were taken once only. It is possible that the number of transient *Pseudomonas*-colonized children in this group actually was greater than that shown by the cultures. The true incidence of infections, on the other hand, was presumably not notably higher than that stated, since a relatively large proportion of these children were hospitalized in the unit a number of times during the period under study and no *Pseudomonas* infections were found in them.

Both the patients admitted newborn and the neurological patient required after operation a considerable amount of handling in connection with suction drainage fluid therapy and feeding, and these manipulations provided an opportunity for the transmission of infection. Patients with oesophageal trepan in particular suffer from copious mucous and urinary postoperative (156) and need repeated bronchial toilettes and suction. During these procedures, *Pseudomonas* flora present in the throat may be conveyed to the lower respiratory passages, where favourable conditions exist for the spread of infection because of the frequently poor respiratory function of these patients. For the same reason, transmission by way of an anaesthesia machine can be assumed to result readily in pneumonia. Colonization of patients with oesophageal trepan may also be promoted by the high humidity conditions necessary in their care (69). Possibly the exceptionally great susceptibility to *Pseudomonas* infections which has frequently been observed in patients with oesophageal atresia (15, 23, 56) and which was evident also in the present series is based on these postoperative factors.

The absence during the studied period of *Pseudomonas* infections in the patients with burns, who are known to be susceptible to this organism, was probably due to the low grade of the burns. Infection with *Pseudomonas* has been found to occur most readily in cases of severe and extensive burns (99)

The *Pseudomonas* infections that occurred in the unit during this investigation were well in agreement with the cases described in the literature with respect to incubation time, symptoms, bacterial findings, duration of illness and prognosis. However in a patient series such as this it often was difficult to ascribe an infectious origin to the symptoms, since poor weight gain vomiting or diarrhoea could well have been associated with the basic disease in many cases. On the other hand occasional cases have been described in which these were the only symptoms of neonatal infection with *Pseudomonas* (22). The symptoms from the respiratory tract could also be readily attributed to the basic pathological condition for example atresia of the oesophagus. For these reasons a part of the *Pseudomonas* colonized newborn infants who actually had symptoms of the infection may have been included in the group of asymptomatic patients, and these cases thus had only the effect of possibly increasing the figure for the mean length of hospitalization of the group of colonized infants. Difficulties were encountered especially in interpreting abdominal distention and vomiting — an ileus type of condition that according to the literature is frequently present also in *Pseudomonas* infections (72-145). These symptoms were erroneously regarded as indications for explorative laparotomy on the suspicion of intestinal obstruction in two patients with pneumonia during the studied period.

Histological changes in the lungs typical of *Pseudomonas* infection were found at autopsy in less than half of the newborn infants who died with definite clinical symptoms of this infection. One of the reasons may have been the difficulty of interpretation of diffuse pneumonia and diffuse haemorrhage in neonates and the fact that specimens for microscopical examination

had not been taken in cases of peritonitis from the most severely infected organ, the intestine. Reports in the literature indicate, however that such changes do not always occur even in definite cases of *Pseudomonas* infection (23, 10).

The high mortality incidence in the diagnosed cases of *Pseudomonas* infection in the newborn series is also compatible with the data in the literature. *Pseudomonas* infection in itself has a high mortality and, in addition infection in general is known to have a poor prognosis in neonates who are in a poor condition and suffer from anomalies (1, 2, 121).

The *Pseudomonas*-colonized newborn infants who died were not all in the poorest category of surgical prognosis, though they included a large number of neonates in the prematures weight range or with one or more congenital anomalies. In the group with oesophageal atresia, 5 children died who can be considered to have been quite good surgical risks (patients No. 1, 5, 10, 11, 15). In these cases the *Pseudomonas* infection should probably be regarded as at least a contributory cause of death. In 4 of these cases the immediate cause was rupture of the anastomosis, but the *Pseudomonas* infection may be said to have promoted the opening of the anastomosis.

Whether the reason for the high mortality especially during the early part of the period under study was a higher virulence of the epidemic strain of *Pseudomonas* prevalent at the time or possibly a more massive contamination is a question that will remain open. The change made in the treatment may well have contributed to the more favourable prognosis in the later period. The marked use of antibiotics possessing a weak action against *Pseudomonas* in the early period may even have promoted the infection (115-177) while the prophylactic administration of colistin and gamma globulin in the later period may have had a part in reducing the number of cases of *Pseudomonas* infection (132).

In the groups of paediatric surgical patients other than those admitted to the unit as newborn, the mortality among *Pseudomonas*-colonized children was fairly low and an infection caused by this organism can be regarded as the

immediate cause of death in two cases only. The prognosis for these two children was poor already because of the basic disease; one patient had a grave congenital heart defect and the other patient had already once earlier undergone an operation for hydrocephalus. The literature however, contains reports of severe *Pseudomonas* infections of septicæmia type in urological patients, especially after operation, with high mortality in some series (55, 56). Even a low grade infection in our urological patients must be considered to have been a risk to life. Furthermore the bacteremia, in some cases of several weeks' duration, prolonged the length of hospitalization and possibly also impaired the surgical result (140).

Klebsiella infections, however, appeared to present a greater problem in the urological patients during the period studied than the *Pseudomonas*. Among neonates, on the other hand, *Pseudomonas* was clearly of greater consequence than *Klebsiella* as the causative agent of hospital infection. In the course of the present study clear indications were obtained of the marked importance

of also other gram-negative rod bacteria as cause of infections, as compared with the formerly so common *Staphylococcus*.

Pseudomonas is known to produce infections with a rapidly fatal course (52) as well as disease conditions of a long duration (50, 52, 55). Presumably for this reason the length of hospitalization of the *Pseudomonas*-colonized children varied over such a wide range that a statistically significant difference from the non-colonized infants could not be established. In individual cases, however, the infection can be said to have prolonged the duration of treatment of newborn infants in the surgical unit. On the other hand, it is difficult to evaluate the effect of *Pseudomonas* colonization in the older children, since most of them were fully symptom-free carriers of the organism and the remainder had rather mild local symptoms of short duration, except for the fatal cases referred to above. Naturally also these infections constituted a certain hazard to the patients.

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Summary

This investigation was undertaken with the object of clarifying the occurrence and significance of the *Pseudomonas* bacillus in the surgical unit of the Children's Hospital of the Helsinki University Central Hospital in the period from October 1 1962 to September 30 1963. During this period a total of 513 surgical paediatric patients, ranging in age from newborn to about 2 years, were treated in the unit.

Pseudomonas bacilli were isolated from 53 of these patients. In 25 cases the children arrived fairly evenly throughout the period studied. The 28 children who became colonized during stay in the unit were on the other hand, mainly concentrated into three periods: October-December 1962, March-April 1963 and August-September 1963.

In bacteriological examinations of hospital equipment, *Pseudomonas* was isolated from, e.g. an anaesthesia machine, the sink and a brush in the unit's kitchen, glass bottles used in the drip-feeding of neonates, and an incubator. The largest number of contaminated objects were found during the first months of the investigation.

The incidences of *Pseudomonas*-colonized children were highest in the groups of neonate and urological patients. Of the newborn 25 per cent were colonized and 16 per cent had symptoms of *Pseudomonas* infection. The organism was isolated from the urine of one-third of the urological patients. The incidence of *Pseudomonas* colonization among the other paediatric surgical patients in the unit was only 5 per cent and the incidence of symptoms of *Pseudomonas* infection was 18 per cent.

The largest group of *Pseudomonas*-colonized neonates was comprised of patients with atresia of the oesophagus. Pneumonia was the most fre-

quent symptom. Infections due to *Pseudomonas* were the most common bacterial infections encountered among the newborn. During stay in hospital *Pseudomonas* infections developed in 14 per cent, those due to *Klebsiella* group rods in 10 per cent and to *Staphylococcus* in 4 per cent of the infants admitted to the unit as newborn.

Seventeen of the *Pseudomonas*-colonized children died, 13 of them had been admitted as newborn. At autopsy a *Pseudomonas* positive culture was obtained from lung samples in 13 cases, in which there also were histological signs of infection. Histological changes specific for *Pseudomonas* infection were found in 5 cases only.

The following conclusions were drawn from the results obtained in this study:

1. A hospital infection type of spreading of *Pseudomonas* bacilli occurred in the ward and operation unit of the paediatric surgical unit of the Children's Hospital during the period of the present investigation.

2. A number of causes apparently were factors contributing to outbreak of the epidemic. During the period studied there were in the unit numerous patients of types susceptible to *Pseudomonas* infection and many who were massive transmitters of infection. The routine hygienic measures in the unit, although well able to prevent spread of *Staphylococcus*, were inadequate for *Pseudomonas*.

3. Transmission of *Pseudomonas* is suspected to have occurred by the hands of the hospital staff and by means of contaminated hospital equipment.

4. *Pseudomonas* infection prolonged the stay in hospital and impaired the prognosis of the paediatric surgical patients, especially of those who had entered the unit as newborn.

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SCANDINAVICA

SUPPLEMENT 196 1969

SOCIAL AND PSYCHOLOGICAL FACTORS
INFLUENCING HOSPITAL ADMISSION
OF CHILDREN

BY GEORG ROSBERG

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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SOCIAL AND PSYCHOLOGICAL FACTORS
INFLUENCING HOSPITAL ADMISSION
OF CHILDREN

BY GEORG ROSBERG

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SOCIAL AND PSYCHOLOGICAL
FACTORS INFLUENCING HOSPITAL
ADMISSION OF CHILDREN

with special reference to mental disorders and
functional symptoms

By
GEORG ROSBERG

*Also published as Supplement No 196 of
Acta Paediatrica Scandinavica 1969*

To my Parents

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Introduction

Since the community must invest considerable capital in hospital buildings, staff salaries and equipment, it is important that hospital beds are used in accordance with conditions laid down for the operation of the hospital. A full understanding of all the reasons why patients are admitted and accepted for admission to hospital is thus important. For children in particular it has been found that admission to hospital cannot always be decided solely on purely medical indications. There are other contributory factors, chiefly social or psychological a combination of the two.

The general hospital system of Finland especially the network of central hospitals, is being constantly enlarged. This requires huge investment. Certain important social considerations are associated & present with the problem of admissions: increasing family employment of the mother, home help facilities provided by the community, housing shortage and small size of homes etc. For these reasons, it was felt that the problem should be studied from the pediatric viewpoint for the whole country within the framework of a comprehensive research project.

When the collection of the present data

was planned in 1962, some investigations had already been carried out in Finland into the effect of social factors and on the need for hospitalization of children (Rantatalo and Valpola 1955, Haavio-Mannila 1962 and Väinänen 1962). The intention was, however in this study, to carry out a close, individual interview on the admission of each patient, complete with statements on discharge from the hospital. The study was launched by a research group and the collection of data was made possible by the kind co-operation of the chief pediatricians and their staffs from twenty-one Finnish pediatric units.

Some preliminary reports have been given from the data collected. Papers were presented at the International Pediatric Hospitalization Symposium in Paris in 1963 (29), at the International Congress of Pediatrics in Tokyo in 1965 (28) and at the first Scandinavian Congress of Social Medicine in Gothenburg in 1967 by Watz Höckert (8).

In the present study the social and psychological factors influencing the hospital admission of children have been analysed with special interest in mental disorders and functional symptoms in childhood. Other aspects have also been analysed and will be published later.

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In the present study, the social and psychological factors influencing the hospital admission of children have been analysed with special interest in mental disorders and functional symptoms in childhood. Other aspects have also been analysed and will be published later.

Review of the literature

a) SOCIO-PSYCHOLOGICAL ASPECTS OF HOSPITAL ADMISSION

In the last ten years there has been keen research especially in the USA, into the social and psychological reasons influencing the approach to community health resources. Many workers have studied the approach to hospitals out-patient clinics, private practitioners and healers, and the reasons for taking this step.

The studies have revealed that women visit hospitals more frequently than men and that the frequency increases among both sexes with age (99). It has also been shown that the utilization of health resources varies in direct proportion to the social class (48). Holders of health insurance policies use medical care facilities especially hospitals (14).

As a rule, these studies have sought to elucidate the social background factors in detail. They have not explained why people seek medical advice, why some delay while others do not, why some consult physicians and others go to healers. The replies to these questions have been sought in various motivation studies, in which the medical behaviour of the public has been studied systematically. A partial reason for the poor results achieved in the studies may be the evident difficulty of establishing objectively measurable quantities in human behaviour and its measurement in the socio-psychological field.

One of the studies in this field that ranks as almost classical is that of Merrill and co-workers (1958) on the attitudes of Californians to poliomyelitis vaccination. They showed that friends, neighbours and the family doctor decided the issue.

Several other factors have also been found to influence the illness behaviour in the diseases of adults (1 23 25 45 47 48 50 52 63 71 85 86 93).

The well-known English field study conducted under the supervision of Spence (1954) showed that there was no correlation between the socio-economic status of the family and the probability of hospital admission for the child. But they found a distinct correlation between the child's hospital admission and maternal capacity. A child whose mother could not manage to care for it was admitted to hospital twice as often as a child whose mother could look after it satisfactorily. The authors considered the mother's ability to care for her child as the decisive factor governing the hospitalization of children. On the other hand, this maternal factor was not important enough to produce a significant correlation with social class.

In many respects the book by Miller and co-workers (1960) was a continuation of Spence's work. Diseases in children were followed for 5 years and 20.4 per cent of the children were admitted to hospital at least once in the 5 years. After the first year a few children had repeated admissions, but there was no significant correlation of admission with the mother's capacity.

One of the most complete and detailed studies of the influence of social and psychological factors on children's hospital admissions was the one carried out by Straus in 1961 among the population of Paris (92). He started from the observation that a considerable number of children were admitted to hospitals in Paris for commonplace diseases. The children were slightly ill, diagnosis produced no

difficulty no special examinations were performed on them and they received no therapy necessitating hospitalization. Straus made an effort to analyse the social and psychological factors affecting the hospitalization of these children.

He first considered the part played by the referring physician, and the decision of the hospital physician which was influenced by the number of beds available. In 65 per cent of the cases in which a child was admitted without the recommendation of a physician, social factors affected the admission. Especially when the child was repeatedly re-admitted a number of social or psychological factors lay in the background. When previous admissions among siblings were studied it was found that if a child had been admitted more than three times, one of its siblings had also been in hospital in 89 per cent of the cases, compared with 44 per cent for the general hospital patient material.

Straus found that housing conditions were the decisive social factor which is readily understandable in a city of the size of Paris, with its slums. One-room dwellings, casual lodgings and inadequate hygiene often led to the admission of children for social reasons. The influence of unfavourable housing was seen most distinctly in those groups admitted without a physician's recommendation, re-admitted repeatedly and always for medically inadequate indications.

Of the other social background factors of the Parisian study it may be mentioned that the family father was often a casual labourer and the family's monthly income was low. These factors were often associated with the housing conditions.

Straus found that the mother's employment outside the home was often dictated by economic necessity and came in the conclusion that gainful employment combined with a large number of children is an important factor of social influence. The author also emphasized that job insecurity discouraged the mothers from staying at home to care for the child, and this made them bring the child to hospital. Fifty per cent of the mothers employed outside the home

entrusted their children to somebody else's care. This solution was almost inevitable when the woman was the sole breadwinner and housing conditions were poor. Among the children under institutional care, the incidence of direct efforts to gain hospital admission (without a medical recommendation) re-hospitalization, and admission on inadequate medical indications was significantly higher.

A review of the statements issued by physicians consulted casually and by the family doctor revealed that social factors were influential in 50 per cent of the former but only 25 per cent of the latter. Straus attributed this partly to the fact that the physician called in casually had not enough authority or hesitated to assume responsibility and was thus more readily inclined to send the child to hospital on his first visit, due to the social and psychological factors he saw.

Straus concluded that the mother's psychic inadequacy — often combined with difficult social conditions — led to the child's admission to hospital.

Another French study was that of Alison et al. (1961) on the background factors of 3,272 children with motor disabilities. In addition to geographical, social and medico-etiological differences, the variations between diagnostic groups were also considered.

Earlier some investigations have been undertaken in Finland on the use of hospital beds for children and the social factors influencing hospital admissions.

Rantasalo and Valpola (1955) established on the basis of their series of 2,151 children treated in the City Hospital of Helsinki, that social factors play a significant role in the hospital admission of children. A greater number of children from families in difficult social conditions were admitted than their proportion of the city population. When common infectious diseases and the age group 7–14 years were omitted, the difference was even more distinct. The role of social factors also appeared clearly in whether the children were admitted from home care or institutional care.

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Review of the literature

a) SOCIO-PSYCHOLOGICAL ASPECTS OF HOSPITAL ADMISSION

In the last ten years, there has been keen research especially in the USA, into the social and psychological reasons influencing the approach to community health resources. Many workers have studied the approach to hospitals out-patient clinics, private practitioners and healers and the reasons for taking this step.

The studies have revealed that women visit hospitals more frequently than men and that the frequency increases among both sexes with age (99). It has also been shown that the utilization of health resources varies in direct proportion to the social class (48). Holders of health insurance policies use medical care facilities, especially hospitals (14).

As a rule these studies have sought to elucidate the social background factors in detail. They have not explained why people seek medical advice, why some delay while others do not, why some consult physicians and others go to healers. The replies to these questions have been sought in various motivation studies in which the medical behaviour of the public has been studied systematically. A partial reason for the poor results achieved in the studies may be the evident difficulty of establishing objectively measurable quantities in human behaviour and its measurement in the socio-psychological field.

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level and the intelligence level indicate the same trend. Inghe also points out that a partial explanation for the accumulation of mental disorders in the lower social classes is perhaps offered by the «down drift hypothesis» advocated particularly by Fara and Dunham (1939) in USA. This hypothesis claims that certain difficulties of adaptation before the illness, and in earlier generations, may result in the degradation of the social class. Inghe found that hereditary factors had received little attention in the studies to date. A long term sedimentation process may be assumed, with earlier generations, which carried the oligophrenic factors, having gradually become over represented in the lower stratum of society.

Stenback and Lehté studied the correlation between mental disorders and social background in the city of Helsinki (1965 and 1966). In their study of the incidence of psychiatric diseases (1965) they analysed the first hospital admission of male patients and found that among 238 cases of psychosis the incidence was lowest in the highest social class. The lowest social class (IV) showed a significantly higher incidence of schizophrenia than the other classes. In their study (1966) of the social classes of 1216 male patients hospitalized for the first time, the same authors found that the age-adjusted annual rates of psychosis and neuroses revealed approximately the same incidence in social classes I, II and III. In the lowest social class the incidence was about twice that of the others. The incidence of schizophrenia was significantly lower in social class I than II. A parallel but not statistically significant difference was seen between classes II and III. The incidence of affective disorders was highest in social class I and lowest in class III.

The studies cited in the foregoing dealt with the correlation between social position and mental disorders in adults. Bearing in mind the stability of the classes in different generations in Finland (Allardt 1964) it may be assumed that the disorders might to some extent be reflected by social classes in children and especially

in adolescents or teenagers. It may also be assumed, naturally, that the mental disorders of the parents are reflected in the children as environmental injuries or possibly hereditary damage.

Heredity has been discussed from this point of view e.g. by Kaila (1950) and Annell (1965). The conclusion reached was that although the mutual relationship of environmental and hereditary effects was very complicated, both mental retardation and psychiatric diseases were based on hereditary predisposition.

Srole and co-workers (1962) tried to throw light on the parental socio-economic background as related to the mental health of the offspring. He took as his basis that the social status of the parents provided a different starting point for the development of each individual, and thus parental social status could be objectively measured. The authors found that the socio-economic position of the parents and the mental health of the offspring were positively correlated. But the role of the greater security enjoyed by the higher social classes for the mental health of the children was unclarified.

Eisenberg (1961) particularly emphasized the importance of prophylactic child psychiatry. He pointed out that the neuro-psychiatric disorders were concentrated in slums. Disorders in the foetal central nervous system may according to Eisenberg result from malnutrition, inadequate prenatal treatment and difficulties of life subject to which the pregnant mother lives. The child's brain may suffer damage due to poor control of infections and the action of toxins. Furthermore, a slum child lives in an environment where it receives little mental stimulation.

In studying the factors which were responsible for children's mental disorders Söderling (1966), starting from common psychosomatic disorders, concluded that a school system, which is foreign to reality may damage the child during the age of development. The complete indifference of higher institutes of learning to the personal problems of young people in puberty, the competition mentality and restrictions imposed on free thinking may in particular damage the

ground factors of children admitted to hospital in South and North Finland Väänänen (1962) showed that the number of children in the family the child's age the seniority of the child among the siblings the marital status of the parents, the size of the home the distance of the home from the hospital the financial standing of the family and the type of community are significant factors in deciding whether or not a child is admitted

Kuusi (1963) while discussing community health services in Finland emphasized that information should be obtained on the health of the population, incidence of diagnosable diseases, composition of patients treated in and outside hospitals consumers of various drugs, etc. On the basis of this information efforts should be made to determine the demands upon various public health and medical services and to outline the future development of community health resources. From the data available it seems obvious that the fundamental weakness in Finnish public health work is the patients' delay in seeking medical advice, which is partly due to the shortage of available medical services in the country.

Morbidity and the need for medical services have also been studied in Finland later (70 76 106)

Kantero and Sorvettula (1965) found that although some parents had read or listened to lectures on child care this did not seem to affect the precautions against anaemia among their children. On the other hand interest in various public health problems appeared to be correlated with the readiness to take the child to hospital but not with the predisposition to illness.

Hultin (1967) studied the influence of the social environment on the somatic development of the child in Finland paying attention to the fact that a difficult social milieu such as poor housing conditions and inadequate nutrition resulted in an increase of respiratory infections and hence an increased need of hospital services. The negative influence of the environment emerges most readily at the age of less than two years. The importance of the foetal period is also very

great in poor social conditions. On the other hand, a good socio-economic environment is no absolute guarantee of good health and sounder development. Improved social environment and higher living standard may result in an increase of consumer goods, tobacco, beverages, and technical auxiliaries all detrimental to health as living standards rise.

b) MENTAL DISORDERS AND HOSPITAL ADMISSION

Social epidemiology of mental disorders has been studied and two extensive investigations concerning adult patients have arrived at apparently different results. Hollingshead and Redlich (36) in 1958 divided the population into five social classes according to the place of residence, the occupation and the education of the head of the family but weighting education most heavily. A comparison of mental disorders with the patients' social status showed no correlation between the incidence of neuroses and social class, the incidence of psychoses in the lowest classes was nearly twice that of the two highest classes and 50 per cent higher than in social class IV. The incidence of schizophrenia increased evenly towards the low end of the grading. Jaco (41) in 1960 correlated the incidence of diseases with occupational position. He found the highest incidence of psychoses and schizophrenia among the unemployed, the professionals and the semiprofessionals. As for education those with 1-4 years of formal schooling had the highest incidence. Following this educational group came the one with an academic degree.

A comparison between Hollingshead's and Jaco's results based on classification by both occupational position and education reveals a contradiction.

Inghe (1959) pointed out the lack of agreement on mental disorders and the contradictory results on the importance of social factors. A point worth making however is the relative agreement on oligophrenia being more common in the lower social classes. Several studies of the relationship between the economic

sense of the word, are originally «class-less». In their own study however they came to the conclusion that the child's social background affected the treatment received in psychiatric disease. This same result was already reported by Hollingshead and Redlich (36) the character of psychiatric therapy was correlated with the patient's social standing.

Lowe (1966) from his study of schizophrenia in early childhood, found that the parents of these children were on a higher occupational level than those of children with other psychic disorders, and that the family of a schizophrenic child was not so often dissolved. Boys were affected with schizophrenia more than twice as often as girls, but the seniority among siblings was not linked with any distinct differences. The author also pointed out potential sources of error for example, parents on a lower educational level do not notice the characteristic behaviour of a schizophrenic child, and therefore fail to seek medical advice. It is possible that these children are finally admitted with an indefinite diagnosis of mental retardation. In trying to trace the etiologic factors, Lowe pays attention to harmony in the family and underlines the coarseness of our yardstick when we measure e.g. divorces, while in reality we should measure the way in which the parents settle their mutual disagreement and the number of points on which they disagree.

Usually in children's diseases and especially in their psychic disorders, attention has been given to the part played by the mother. Mastropalo (1967) from his study of juvenile delinquents, came to the conclusion that the father's role in mental disorders is highly significant. The father/son relationship, as the author demonstrates, is directly connected with the background of the disturbed behaviour of juvenile delinquents. An absent or weak father figure has a detrimental effect on the development of the son's character. In practice, the father's role is to set an example for the son and to teach correct behaviour patterns. If the father is unable to assume this role, or is otherwise out of balance the result may be

maladjustment of the son. The father should also be able to lead the normal antagonism which exists in boys in pre puberty and puberty into their right channels, so that it would not be released by rebelling against the laws and accepted morals of the community.

Some authors have concentrated on certain aspects of the family crisis with a retarded child before institutionalization — in the situation where hospital admission is a possibility. Saenger (1960) found that persons committed to an institution for the retarded tended to have lower intelligence, were more likely to come from an ethnic minority and had required more time and attention from family members than those who were not institutionalized. Behaviour problems, hyperactivity aggression or sexual maladjustment were the most important factors leading to commitment. Farber (1959) found that willingness to place a retarded child in an institution was related in a complex way to the sex of the child, the social status and religion of the family and the marital integration of the parents. Mercer (1967) pointed out in his study of patterns of family crisis related to reacceptance of the retarded that there are two crisis patterns: the burden-of-care crisis and the interpersonal structural stress crisis. All families are equally likely to report the latter but families who leave their retardates in the institution are more likely to report the former.

Grad and Salisbury (1966) discussed the difficulties a mentally ill family member causes at home and the chances of treating a mentally ill patient at home. Sending a mentally ill patient to hospital is a difficult problem for the family. There is no doubt that many families would prefer to keep the patient at home, even though there may be difficulties and excessive burdens of work. The authors restricted themselves completely to adult psychiatric cases. In the event of mentally ill children, the mother's feelings of guilt, mutual controversies inside the family, the parents' desire to protect the child and to counter their subconscious feelings of guilt and self-pity should also be taken into consideration.

developing psyche. The author also devoted attention to the negative aspects of strictly dogmatic and narrow religious mind for the developing psyche. A home which lays excessive emphasis on religion arousing fear in the children and making exaggerated demands on them damages the growing psyche and this damage is reflected in the need for psychic therapy.

In Finland Frak (1968) dealt with the numerous problems of teenagers. Of these problems can be mentioned various psychiatric, psychosomatic and social disorders and behind them both psychophysical development and «circulus vitiosus» between this and neighbourhood.

Tizard (1966) devoted attention to the important role of mental subnormality in child psychiatry and to the difficulty of distinguishing, especially in children between mental retardation and definite child psychiatric diseases. The author also emphasized that no universally accepted classification of children's mental disorders is available. Nor has the incidence of mental disorders among children been studied in detail any more than has the number of children requiring the help of child guidance clinics.

Eaton (1967) pointed out that most diagnoses of emotional disturbances in children can be made on an outpatient basis. Hospitalization for diagnosis is, however, preferable when the admitting physician may require factual reporting of symptomatic behaviour or want to determine whether the child will or can behave differently if offered opportunity in an accepting supporting relatively neutral environment. He may also want to further evaluate and elaborate outpatient data when this information is inconclusive.

Eaton also stressed that hospitalization for treatment is indicated when the child is dangerous to himself or others, or when his behaviour has become intolerable to his home or community. It is also indicated when outpatient therapy is failing or when habit training at home has been unsuccessful and the parents are too involved in the negative cycle to handle the problem constructively themselves.

MacDermott and co-workers (1967) underlined the same diagnostic difficulty and lack of classification. The writers said that there are no standard tests for mental disorders, the psychiatrist himself is the diagnostic instrument. In their own study, on American children the authors were unable to show any statistically significant difference in childhood psychoses between the occupational groups. They came to the conclusion that the composition of the material was a result of selection and that the upper socio-economic groups had better medical facilities available and paid more attention to the abnormal behaviour of their children. The upper classes can obtain private treatment for their children while the lower classes must consult community health resources. Parents may prefer to have their psychotic children diagnosed and masked as mentally retarded since it is often easier to find special education for the retarded than for mentally diseased children. The authors pointed out that children's maladjustment was based on acquired habits and behaviour inside the family.

Miller et al (1960) stressed in their book that parents seldom consulted a physician for enuretics until the child was 5 years old. The distribution of the cases of enuretics among the social classes revealed the most pronounced correlation between low social status and neglected physical care. Matrimonial instability, loss of one of the parents, and criminalism of the parents were most markedly correlated with enuretics.

The authors also studied maladjustment of the child and found no statistically significant correlation to any environmental factor such as the stability of the family or poor social conditions. Among the factors concerned with the child age was found to be of the greatest importance, in that maladjustment of long standing was most common among children over three years of age. Another personal factor was the sex: the incidence among boys was twice as high as among girls.

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Material and methods

As mentioned, the collecting of the data was carried out in 1962 by preparing a comprehensive questionnaire of 70 selected questions¹ (Appendix) to be completed in different hospitals simultaneously. Only two children's wards, Tam-

per Central Hospital in middle west Finland (66 beds) and a children's hospital (Åboland Sjukhus) in Turku (30 beds) which serves the archipelago on the southwest coast, could not participate for local reasons. All the other 21 children's departments in the country were included in the study (Fig. 1). The prospective method was used, having considerable advantages compared with the retrospective method in this type of data collection (44-46). A meeting of the head physicians of all participating 21 children's hospitals was held and more detailed instructions for the study were given.

The study was conducted in three phases: the first in April and May 1963, the second in August 1963 and third in January 1964, in order to reflect the mean situation of the year of investigation. The series consisted of a total of 7954 child patients, divided into three phases presented in Table 1. The total number of beds for children in the participating hospitals was 1462 and the total number of children treated in them in 1963 was 28,635. The present material covered 27.8 per cent

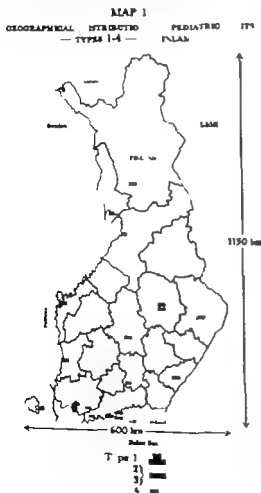


TABLE 1

DISTRIBUTION OF THE MATERIAL BY PERIODS OF THE STUDY

	Number of admissions	Per cent
First period	4521	56.8
Second period	999	12.6
Third period	2434	30.6
Total	7954	100.0

by Aulo Hallman, M.D., Ole Wenz Höckert, M.D., and Eero H. Valanne, M.D., with consultative assistance of Elina Haavio-Mannila, Dr. Pol. Sci.

Purpose of the study

- I The first purpose of the present study was to find out the factors connected with child home and hospital which constituted the social or psychological indications influencing the hospital admission of children
- II The second purpose was to elucidate socio-economic and socio-psychological background factors in the diagnosis groups of mental disorders and so called functional symptoms of children

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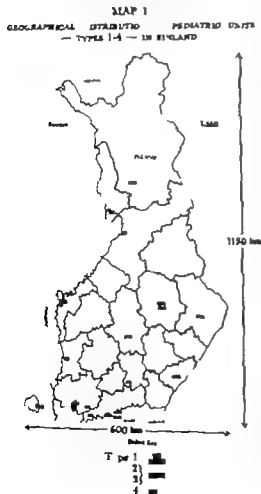


TABLE 1

DISTRIBUTION OF THE MATERIAL BY PERIODS OF THE STUDY

	Number of admissions	Per cent
First period	4321	54.8
Second period	999	12.6
Third period	2634	33.6
Total	7954	100.0

by Aulo Hallanen, M.D., Olo Wess-Hoekert, M.D. and Eero H. Väänänen, M.D. with collaborative assistance of Elina Haavio-Mannila, Dr. Pol. Sci.

of all children admitted to hospital in Finland during the whole year (Table 2). The sample consequently represents a period of one year.

Table 2 shows the distribution of the sample according to hospital and for comparison the same for all the children admitted during 1963. The percentages of completed questionnaires out of the total number of admissions are presented.

The central hospitals treat some groups of children in wards other than the pediatric, such as child patients undergoing surgery or those with ophthalmic, otologic and dermatologic diseases. The study only covered the patients of the pediatric wards, although e.g. Children's Hospital

of the University of Helsinki and the City Hospital of Helsinki included pediatric surgical patients in their series.

Completing of the questionnaire

The first 39 questions dealing with socio-economic and socio-psychological factors in the family were completed by nurses and social workers or in teaching hospitals, by interns with the help of medical students in connection with the admission of the child. The information was supplied in the majority of the cases by the mother who usually brought the child to hospital (Table 3).

The questions dealing with parents' attitudes (Nos 40-44) were filled in by ward nurses when the child was dis-

TABLE 2

BEDS AND ADMISSIONS OF CHILDREN IN THE PARTICIPATING HOSPITALS, AND THE NUMBER OF ADMISSIONS IN THE PRESENT SERIES WITH PERCENTAGES VERSUS TOTAL ADMISSIONS TO RESPECTIVE HOSPITAL

Hospital	Beds for children 1963	Admissions in 1963	Present series		
			Number of admissions	Per cent	Per cent of all admissions in each hospital
1 Children's Hospital, University of Helsinki	270	5968	1458	18.1	24.1
2 Children's Hospital, University of Turku	70	1807	450	5.7	24.9
3 Children's Castle, Helsinki	200	1330	376	4.7	28.3
4 City Hospital of Helsinki (Aurora)	166	2663	1232	15.5	46.3
5 Lapland Children's Hospital, Rovaniemi	110	2388	796	10.0	33.3
6 Savo Children's Castle, Kuopio	80	1016	326	4.1	32.1
7 North Karelia Central Hospital, Joensuu	56	674	292	3.7	43.3
8 South Saimaa Central Hospital, Lappeenranta	47	1433	416	5.6	31.1
9 Central Finland Central Hospital, Jyväskylä	41	1833	462	5.8	25.2
10 Central Hospital, Kuopio	44	1293	174	2.2	13.5
11 Central Hospital, Vaasa	38	830	241	3.0	28.4
12 Central Hospital, Savonlinna	25	394	140	1.8	35.6
13 Central Hospital, Kemi	23	738	113	1.4	15.3
14 City Hospital for Infectious Diseases, Turku	68	861	264	3.3	30.7
15 Provincial Hospital, Mikkeli	49	1108	253	3.2	22.8
16 City Hospital, Lahti	38	792	232	3.2	31.8
17 Provincial Hospital, Oulu	37	888	278	3.5	31.3
18 Provincial Hospital, Hämeenlinna	28	686	44	0.6	6.4
19 Provincial Hospital, Pori	27	755	173	2.2	23.2
20 District Hospital, Salo	15	608	128	1.6	21.1
21 Provincial Hospital, Tammihaar	15	195	31	0.6	26.2
	1452	28635	7931	100.0	27.8

TABLE 3

PERCENTAGE AGE DISTRIBUTION THE MATERIAL BY SOURCE INFORMATION, OR THE PERSON WHO BROUGHT THE CHILD TO HOSPITAL

	Per cent
Mother	72.0
Father	12.4
Both parents	8.4
Non-relative person	2.4
Other relative	1.8
Child personally	1.0
Not known	2.0
	100.0

changed from the hospital. The nurses had several opportunities to make observations on the parents' attitudes e.g. during visiting hours.

The last six items dealing with diagnosis and some hospital factors were completed by the physician in charge of the ward when the patient was discharged. The physician made his judgement for each case as a whole taking into consideration the whole hospitalization period.

By final diagnosis was meant the disease which resulted in hospital admission. The final diagnosis was a conclusion reached in the ward. The admission diagnosis could be only tentative.

In the present material the classification by diagnosis was made using the final diagnosis. Four-digit figures of the international nomenclature of diseases (WHO 1948) were used as the diagnosis numbers in the questionnaire¹.

Because of lack of other generally accepted nomenclature the WHO nomenclature was used but it may be incomplete and is only symptomatic not etiological.

Although the distribution tables carry the official WHO nomenclature used in the present study to make comparisons with official statistics from both here and abroad possible, other classifications of diagnoses (especially in child psychiatry)

such as diagnosis by etiology or by severity or grade of the disorder would actually convey more.

Distribution of the material by indications for admission based on hospital physician's opinion is seen in Table 4

TABLE 4

DISTRIBUTION OF THE PRESENT SERIES BY INDICATION FOR DELUSION

	Number of admissions	Per cent
Purely medical indications	7159	90.8
Partly or decisively social reasons	552	7.0
Psychological factors in the family	176	2.2
Total	7887	100.0
Indication unknown	64	
All together	7951	

Social and psychological factors

In the present study *social factors* influencing the admission of children to hospital were those additional factors preventing adequate home care and the result of difficult socio-economic background.

The *psychological mechanisms* in the hospital admission of children might consist of following factors (79)

- the parental psychological tolerance limit
- the readiness of the referring physician to pass the child on
- the physician's own burden of work
- his lack of examination facilities
- his lack of familiarity with pediatrics
- his readiness to be influenced by the social and psychological factors in the family of the child
- the hospital physician

¹As known the WHO nomenclature was modernized and renewed in 1968.

of all children admitted to hospital in Finland during the whole year (Table 2) The sample consequently represents a period of one year

Table 2 shows the distribution of the sample according to hospital and for comparison, the same for all the children admitted during 1963 The percent ages of completed questionnaires out of the total number of admissions are presented.

The central hospitals treat some groups of children in wards other than the pediatric, such as child patients undergoing surgery or those with ophthalmic, otologic and dermatologic diseases The study only covered the patients of the pediatric wards although e.g. Children's Hospital

of the University of Helsinki and the City Hospital of Helsinki included pediatric surgical patients in their series

Completing of the questionnaire

The first 39 questions dealing with socio-economic and socio-psychological factors in the family were completed by nurses and social workers or in teaching hospitals, by interns with the help of medical students in connection with the admission of the child The information was supplied in the majority of the cases by the mother who usually brought the child to hospital (Table 3)

The questions dealing with parents attitudes (Nos 40-44) were filled in by ward nurses when the child was dis-

TABLE 2

BEDS AND ADMISSIONS OF CHILDREN IN THE PARTICIPATING HOSPITALS, AND THE NUMBER OF ADMISSIONS IN THE PRESENT SERIES WITH PERCENTAGES VERSUS TOTAL ADMISSIONS TO RESPECTIVE HOSPITAL

Hospital	Beds for children 1963	Admissions in 1963	Present series		
			Number of admissions	Per cent	Per cent of all admissions in each hospital
1 Children Hospital, University of Helsinki	270	5968	1458	18.1	24.1
2 Children Hospital University of Turku	70	1807	450	5.7	24.9
3 Children's Castle, Helsinki	200	1330	376	4.7	28.3
4 City Hospital of Helsinki (Aurora)	166	2663	1232	15.5	46.3
5 Lapland Children Hospital, Rovaniemi	110	2368	796	10.0	33.3
6 Savo Children's Castle, Kuopio	80	1016	326	4.1	32.1
7 North Carelia Central Hospital, Joensuu	56	674	292	3.7	43.5
8 South Saimaa Central Hospital, Lappeenranta	47	1433	446	5.6	31.1
9 Central Finland Central Hospital, Jyväskylä	44	1833	462	5.8	25.2
10 Central Hospital, Kuopio	44	1293	174	2.2	13.5
11 Central Hospital, Vaasa	38	830	241	3.0	28.4
12 Central Hospital, Savonlinna	25	594	140	1.8	3.6
13 Central Hospital, Jämsä	25	758	113	1.4	15.3
14 City Hospital for Infectious Diseases, Turku	68	861	264	3.3	30.7
15 Provincial Hospital, Mikkeli	49	1108	253	3.2	22.8
16 City Hospital, Lahti	38	792	252	3.2	31.8
17 Provincial Hospital, Oulu	37	888	278	3.5	31.3
18 Provincial Hospital, Hameenlinna	28	686	44	0.6	6.4
19 Provincial Hospital, Pori	27	735	175	2.2	23.2
20 District Hospital, Salo	15	608	128	1.6	21.1
21 Provincial Hospital, Tammenlahti	1	195	51	0.6	26.2
	1452	28635	7931	100.0	27.8

Mental disorders constituted the first group (Table 6). The second group, functional symptoms reflected the group where the admission took place without any other diagnosis than symptomatic. Diagnoses such as e.g. icterus, hepatomegalia, dehydration and albuminuria, which indicated organic disorder without etiologic diagnosis, were excluded. The third group included all other admitted patients.

As pointed out by MacKeith (1961) it is difficult in childhood to distinguish between the somatic diseases, the mental disorders and the diseases which may be termed psychosomatic, and to demonstrate that psyche is a background factor contributing to the manifestation of a

disease. It could be presumed that a psychologically unfavourable environment (quarrelsome family life economic difficulties, frequent illness at home) may be one of the factors contributing to the outbreak of illness in a child. In this case, it could be assumed that the manifestation and symptoms would be hard to diagnose in specific terms. Recurrent attacks of abdominal pain, constipation, encopresis, enuresis, certain forms of asthma, headache are examples of childhood diseases customarily referred to this group.

On the basis of the foregoing, the functional symptoms group of the present series (Table 7) can perhaps be taken to reflect psychosomatic diseases to a cer-

TABLE 6

DISTRIBUTION OF THE MENTAL DISORDERS GROUP

Diagnosis (International nosomenclature of diseases Nos. 300—326)	Number	Per cent
Habitus abnormalis infantum	58	21.9
Oligophrénia ataxia	43	18.2
Maladaptatio aetatis	27	10.4
Enuresis, encopresis, somnambulismus indicata	20	7.5
Instabilitas emotionalis	15	5.8
Resectio hysterica, fractus angustiae nondefinitus	12	4.5
Deficientia intelligentiae	11	4.2
Dyslexia, dysphasia primaria	11	4.2
Resectio angustiae	10	3.8
Mongolismus	8	3.0
Idiotia	8	3.0
Dyslexia minorcerebralis	7	2.6
Debilis	6	2.3
Schizophrenia latens, psychosis schizoaffectiva	5	1.9
Psychosis non definita	5	1.1
Psychoneurosis aliae non definitae	5	1.1
Resectio hypochondriaca	2	0.8
Resectio phobica	2	0.8
Others	14	5.3
Total series	283	100.0

TABLE 7

DISTRIBUTION OF THE FUNCTIONAL SYMPTOMS GROUP

Diagnosis (International nosomenclature of diseases Nos. 780—785.0, 785.1—6, 786.9 and 790—795.5)	Number	Per cent
Observationes et explorationes non causae definitae alii	183	33.2
Observationes non definitae	115	19.2
Colica non definita, doloris abdominalis nondef.	102	17.3
Observationes et explorationes non causae non definitae	47	8.0
Cephalalgia non definita	16	2.7
Incontinentia alvi	14	2.4
Observationes et explorationes non causae recalesc.	14	2.4
Nausea, vomitus	11	2.2
Motus abnormalis locomotionis	12	2.1
Encephalopathia non definita	5	0.9
Lactio normalis	5	0.9
Incontinentia urinae non definita	5	0.9
Anorexia non definita	4	0.7
Other neurological symptoms	17	2.9
Others	26	4.5
Total series	548	100.0

ians decision for admission

- availability of beds in the hospital
- children coming without reference with an unknown background, whom he dares not send home
- the reference suggests a serious diagnosis which must be verified or excluded
- readiness to be influenced by the social and psychological background

All these factors were summarized as «psychological factors» in the present study

The physician's replies to the questions probably also reflected to some degree the prevailing attitudes among the pediatricians of Finland and their understanding of the social and psychological background of their patients

In considering the samples with respect to freedom from bias the part played by the fact that the estimates of parental attitudes were based on the subjective appraisal of the nurses must be borne in mind

Finnish nurses are trained in psychology and the ward nurses who completed the questionnaire on the child's discharge from hospital have a lot of experience of the hospital milieu and human behaviour

The fact that the study was carried out in twenty-one hospitals and numerous wards tends to counterbalance distortion in the appraisals (e.g. too subjective or tinged by the observer's own psychic difference) of an individual nurse. There were of course nurses who owing to their other obligations had no time to devote to an accurate assessment of each family and fathers whom the nurses never saw at all. But even the fact that the father did not pay a single visit to his child in the hospital may reflect his attitude to the child

Hospital nurses do tours of duty. It is possible that some of the ward nurses

completing the form did not happen to be on duty when the parents visited their child. Visiting hours in 1963–64 in Finnish hospitals were restricted and relatively short: one to three hours.

Classifications of some background factors

The hospitals were divided as follows, primarily according to their working facilities and operation (Fig. 1 and Table 2)

- 1 University teaching hospitals (Helsinki and Turku) and a special hospital treating patients from the whole country (The Children's Castle in Helsinki)¹
- 2 City Hospital of Helsinki (Aurora) whose patients were from a narrow limited metropolitan area, with some half a million of inhabitants.
- 3 Pediatric units with two or more pediatricians.
- 4 Pediatric units with one pediatrician only

Four sets of hospital factors were selected for closer studies: hospital resources in different geographical parts of the country, type of hospital, waiting time for admission and those factors which delayed the discharge of patients

Classification by diagnosis The patients were divided into three major groups according to the final diagnosis (Table 5)

TABLE 5

DISTRIBUTION OF THE PRESENT SERIES INTO GROUPS ACCORDING TO THE FINAL DIAGNOSIS

Diagnostic groups and numbers ²	Number of diagnoses	Per cent
Mental disorders Nos. 300–326	263	3.5
Functional symptoms Nos. 780–785.0, 785.5–6 786.9 and 790–793.5	588	7.4
Other diseases	7101	89.5
Total	7954	100.0

¹ This pediatric medical center treats especially three groups of diseases: cerebral palsy, mental disorders and premature infants. (Professor Arvo Ylppö, M.D., was head of the hospital at that time.)

² Numbers according to the international WHO nomenclature of diseases (1948)

Mental disorders constituted the first group (Table 6). The second group, functional symptoms, reflected the group where the admission took place without any other diagnosis than symptomatic. Diagnoses such as e.g. icterus, hepatomegaly, dehydration and albuminuria, which indicated organic disorder without etiologic diagnosis, were excluded. The third group included all other admitted patients.

As pointed out by MacKeith (1961) it is difficult in childhood to distinguish between the somatic diseases, the mental disorders and the diseases which may be termed psychosomatic, and to demonstrate that psyche is a background factor contributing to the manifestation of a

disease. It could be presumed that a psychologically unfavourable environment (quarrelsome family life, economic difficulties, frequent illness at home) may be one of the factors contributing to the outbreak of illness in a child. In this case, it could be assumed that the manifestation and symptoms would be hard to diagnose in specific terms. Recurrent attacks of abdominal pain, constipation, encopresis, enuresis, certain forms of asthma, headache are examples of childhood diseases customarily referred to this group.

On the basis of the foregoing, the functional symptoms group of the present series (Table 7) can perhaps be taken to reflect psychosomatic diseases to a cer-

TABLE 6

DISTRIBUTION THE MENTAL DISORDERS GROUP

Diagnosis (International nomenclature of diseases Nos. 300—326)	Number	Per cent
Habitus abdominalis infans	58	21.9
Oligophtalmia alba	43	16.2
Maladaptatio acuta	27	10.2
Emuresis, pernoctum lanocturnum nocturnum	20	7.5
Instabilitas emotionalis	15	5.6
Reactio hysterica, reactio angoris nondefinita	12	4.5
Deficientia intelligentiae	11	4.2
Dyslexia, dysphasia primaria	11	4.2
Reactio angora	10	3.8
Meningitis	8	3.0
Idiotia	8	3.0
Dyslexia neurocirculatoria	7	2.6
Debilis	6	2.3
Schizophrenia latens, psychoses schizoaffectiva	5	1.9
Psychosis non definita	3	1.1
Psychoneurosis alba non definita	3	1.1
Reactio hypochondrica	2	0.8
Reactio phobica	2	0.8
Others	14	5.3
Total series	265	100.0

TABLE 7

DISTRIBUTION THE FUNCTIONAL SYMPTOMS GROUP

Diagnosis (International nomenclature of diseases Nos. 780—785.0, 785.5—6, 786.9 and 790—795.5)	Number	Per cent
Observationes et explorationes casus definitae alii	195	33.2
Convulsiones non definitae	113	19.2
Colica non definita, dolor abdominalis nondescriptus	102	17.3
Observationes et explorationes casus non definitae	47	8.0
Cephalalgia non definita	18	2.7
Incontinentia alvi	14	2.4
Observationes et explorationes casus mentales	14	2.4
Nausea, vomitus	13	2.2
Motus abnormalis involuntarius	11	2.0
Encephalopatia non definita	5	0.9
Lacrimatio	5	0.9
Incontinentia urinae non definita	5	0.9
Anorexia non definita	4	0.7
Other neurological symptoms	17	2.9
Others	28	4.3
Total series	588	100.0

tain extent. The group also measures the parental desire to have their child examined for symptoms on the basis of which the physician failed to give a specific diagnosis. The group thus indicates also the cases in which the physician encountered the greatest diagnostic difficulties.

*Convulsiones non definitae covered mainly fever and affect cramps, generally cramps in which no definite disease could be found and were included in the group of functional symptoms. Neurologically verified epilepsy was graded elsewhere. Some hospitals may of course have given this symptomatic number to conditions which were dubiously epileptiform cramps but most indefinite cramps in the present series did obviously not represent epilepsy.

Classification by socio-economic factors
The material was divided according to some factors, in order to estimate the influence of social status or hospitalization

The variables selected were parental income, the father's occupational position, educational level, and marital status; number of inhabitants per room; type of child's domicile; and distances from home to the nearest physician and hospital. An attempt was made to study the mutual correlations of some recorded factors.

Such factors as mother's health, mother's employment outside home, ownership of a private car, a TV set or a summer house were not classified as purely socio-economic factors but were considered more as socio-psychological factors.

Parents' readiness to seek admission to hospital for their child was studied by means of the following variables: admission delay for economic reasons, did the parents seek medical advice in time, had the child been neglected at home, had the child been hospitalized previously for the same disease, had the mother father or any of the siblings been admitted to hospital.

TV-ownership and socio-economic level of the family

To see how TV ownership correlated with the general socio-economic level of

the family correlation analysis of certain variables associated with the concept of «socio-economic level» was carried out to throw light on the concept. The variables used for the farming population were the following

- 1 ownership of television
- 2 disposable living space (number of rooms per inhabitant)
- 3 cultivated field area

For non farmers the variables were

- 1 ownership of television
- 2 disposable living space
- 3 income level
- 4 father's educational level

For both population groups, the variables were dichotomized and correlated mutually (phi-coefficient)

Table 8 shows that for the farming population the area of field under plough definitely measures a different concept from that measured by TV-ownership and disposable living space which showed a moderate degree of mutual correlation (.59) and were apparently associated with the status concept. Among non farmers the correlation was highest between income level and father's educational level (.47) which were clearly associated with the concept of socio-economic status, but perhaps with urbanization also. It may be pointed out that the ownership of TV which was considered a variable associated with enlightenment hardly correlated at all with the father's educational level among non farmers.

TABLE 8
NUMBER OF CASES OF SOCIOPATHICITY BY TYPE
VARIABLE

$ \begin{array}{r} 2 \mid 59 \\ 3 \mid 08 \quad 09 \\ \hline 1 \quad 2 \end{array} $ <p>Farmers</p>	$ \begin{array}{r} 13 \\ 4 \mid 22 \quad 11 \\ 5 \mid 07 \quad 10 \quad 42 \\ \hline 1 \quad 2 \quad 4 \end{array} $ <p>Non-farmers</p>
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Intercorrelation of some other variables

The intercorrelation of father's occupational status and parental income was also calculated. The phi-coefficient was 0.394. The intercorrelation was also determined between car ownership and parental income. It was 0.284. Cross-tabulation of summer cottage ownership and parental income showed an intercorrelation of 0.214. All this showed that the intercorrelation between father's occupational status, car ownership and summer cottage ownership was not very strong.

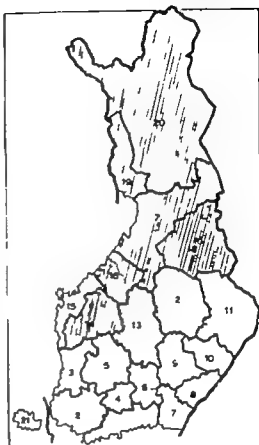
Geographical distribution. In an effort to study whether hospital conditions and general medical facilities were of importance in children's admission to hospital, it was found best to divide the geographical territory covered by the present study into two parts as widely different from each other as possible in community health resources.

Some central hospital districts of north and east Finland are in a poorer position than southern districts (26 74 103 104 106). The factors selected to measure the health resources of the region were the density of physician per 10 000 density of hospital beds per 1000 head of population and hospital visits of children per 1000 head of population (Table 9). The division is shown in Fig. 2. The territory with poorer community health resources was called North Finland and the better equipped territory South Finland for the purposes of this study.

Classification by the type of community
The distribution by type of community can be made on various grounds. The material can be divided into an urban

and rural population. However urban communities were divided into Helsinki and other towns, since Helsinki, a small

MAP 2
GEOGRAPHICAL DISTRIBUTION BY CENTRAL HOSPITAL
DISTRICTS INTO NORTH AND SOUTH ISLAND



Shaded area = North Finland
White area = South Finland

TABLE 9

	Physicians per 10 000 inhabitants in 1963	Hospital beds per 1000 inhabitants in 1963	Hospital visits of children per 1000 inhabitants in 1960
North Finland	3.7	3.6	54.2
South Finland	6.7	4.4	51.1

metropolis, represented a special type of urban settlement and had in addition the best health resources in Finland. The rural areas were divided into urbanized districts (= market boroughs) and rural districts

proper. The latter division did not perhaps reflect very distinct differences as the difference between some industrialized rural centres and small urban districts may be narrow (4).

Statistical techniques

The statistical test applied was the chi-square test for fourfold table, with Yates' correction for continuity. The fourfold tables were formed by cross-tabulation of, for instance, psychological/other admissions and legitimacy/illegitimacy. A respective test was carried out for the social admissions (social/other admissions vs. legitimacy/illegitimacy). In some cases, several classes were combined into one for testing; this is indicated in the tables.

Three levels of significance were used

- = highly significant ($p \leq 0.001$)
- = significant ($0.001 < p \leq 0.01$)
- = almost significant ($0.01 < p \leq 0.05$)

The asterisks corresponding to one test appear after two percentage figures, namely the percentages of indication (or disease) type in both classes of the background factor in question.

The phi coefficient of correlation (McNemar 1955, pp. 202-203) was applied in measuring the degree of co-variation between dichotomized socio-economic status variables.

The data were processed in the Computer Center of University of Oulu with an Elliott 805 computer.

As was shown e.g. by Feldstein and Butler (1965) in their paper, the study of an individual social factor or the study of several factors separately does not provide the correct picture of the mutual relations. Many factors are more or less interdependent. In order to reach a result as close to reality as possible, the mutual relations of the factors must be taken into account. This is best achieved using multivariate analysis.

In the present study however multivariate analysis was not used mainly because of lack of sufficient experience about this type of studies. It must be borne in mind throughout, however, that the factors can be mutually interdependent.

Results

1

SOCIAL AND PSYCHOLOGICAL FACTORS IN THE HOSPITAL ADMISSION OF CHILDREN

Factors connected with the child

SEX

Of the child patients of the present series, 43.3 per cent were girls and 56.7 per cent boys.

A study of the group in which psychological indications affected admission to hospital reveals that the group consisted of 38.6 per cent girls and 61.4 per cent boys. In the social indications group the corresponding distribution was 41.4 per cent girls and 58.6 per cent boys.

A comparison of whether psychological or social indications affected the admission

of boys more often than that of the girls revealed no significant differences.

When the percentages of the sexes in the age groups of the present study and in those of the total Finnish population are compared, the overrepresentation of boys emerges distinctly (Table 10)

LEGITIMACY

4.3 per cent of the children of the present study were born out of wedlock, while 95.7 per cent were legitimate.

The frequency of psychological indications was not significantly different in legitimate and illegitimate children.

Social indications were more frequent for the illegitimate than the legitimate children. The difference was highly significant ($\chi^2 = 150.72$ $p < 0.001$) (Table 11)

TABLE 10

DISTRIBUTION OF THE MATERIAL BY SEX AND AGE COMPARED WITH TOTAL POPULATION OF CHILDREN IN FINLAND IN 1963 AND 1964

Age group 0-1 years

	Present study		All Finland 1963		All Finland 1964	
	N	%	N	%	N	%
Girls	1113	42.8	39 351	48.9	38 687	48.9
Boys	1485	57.2**	41 264	51.1	40 446	51.1
Total	2598	100.0	80 615	100.0	79 133	100.0

Age group 2-6 years

	Present study		All Finland 1963		All Finland 1964	
	N	%	N	%	N	%
Girls	1415	42.7***	233 501	49.0	234 078	49.0
Boys	1898	57.3**	243 144	51.0	243 401	51.0
Total	3313	100.0	480 645	100.0	477 479	100.0

Age group 7-15 years

	Present study		All Finland 1963		All Finland 1964	
	N	%	N	%	N	%
Girls	831	45.4	399 896	49.1	390 829	49.0
Boys	999	54.6*	415 896	50.9	407 078	51.0
Total	1830	100.0	815 792	100.0	798 005	100.0

metropolis represented a special type of urban settlement and had in addition the best health resources in Finland. The rural areas were divided into urbanized districts (= market boroughs) and rural districts

proper. The latter division did not perhaps reflect very distinct differences as the difference between some industrialized rural centres and small urban districts may be narrow (+)

Statistical techniques

The statistical test applied was the chi-square test for fourfold table, with Yates' correction for continuity. The fourfold tables were formed by cross-tabulation of, for instance, psychological/other admissions and legitimacy/illegitimacy. A respective test was carried out for the social admissions (social/other admissions vs. legitimacy/illegitimacy). In some cases, several classes were combined into one for testing this is indicated in the tables.

Three levels of significance were used

- * = highly significant ($p \leq 0.001$)
- = significant ($0.001 < p \leq 0.01$)
- = almost significant ($0.01 < p \leq 0.05$)

The asterisks corresponding to one test appear after two percentage figures, namely the percentages of indication (or disease) type in both classes of the background factor in question.

The phi coefficient of correlation (McNemar 1953, pp. 202-203) was applied in measuring the degree of co-variation between dichotomized socio-economic status variables.

The data were processed in the Computer Center of University of Oulu with an Elliott 803 computer.

As was shown e.g. by Feldstein and Butler (1965) in their paper the study of an individual social factor or the study of several factors separately does not provide the correct picture of the mutual relations. Many factors are more or less interdependent. In order to reach a result as close to reality as possible, the mutual relations of the factors must be taken into account. This is best achieved using multivariate analysis.

In the present study however multivariate analysis was not used, mainly because of lack of sufficient experience about this type of studies. It must be borne in mind throughout, however, that the factors can be mutually interdependent.

SENIORITY AMONG SIBLINGS

The only child of the family was in question in 25.9 per cent of the admissions. 14.1 per cent were eldest children.

Tests were carried out in two sets first, only child versus others and second eldest child versus others.

In psychological indications, no significant difference existed in the case of the only child or the eldest child in other words, psychological factors did not affect the admission of the only or the eldest child any more often than they affected that of the other children.

Social indications affected the child's admission more often when the only child was involved than when the child was one of several siblings. The difference was highly significant ($\chi^2 = 21.50$ $p < 0.001$) Table 12.

Factors connected with home and family

MOTHER'S EMPLOYMENT

33.1 per cent of the mothers of the children in the present study were employed outside the home. 30.2 per cent worked full-time and 4.9 per cent were employed part-time.

A comparison of the frequencies of psychological and social indications for hospital admission between the mothers

employed outside home and those staying at home revealed no significant differences.

When the full time employed mothers were tested against all others there were more social indications in the full time working group than in the others. The difference was highly significant ($\chi^2 = 149.0$ $p < 0.001$) Table 13.

MOTHER'S STATE OF HEALTH

92.5 per cent of the children had a healthy mother while 7.5 per cent had a sick mother or a mother in poor physical condition.

The frequency of psychological factors did not differ between the healthy and the sick or physically poor-condition mothers.

Additional social factors contributed to hospital admission more often when the mother was sick or in poor physical condition than when she was healthy. The difference was highly significant ($\chi^2 = 26.92$ $p < 0.001$) Table 14.

INCOME OF PARENTS

40.2 per cent of the parents in the present series were in the income bracket below 600 mk/month. 15.6 per cent of the parents made more than 1000 mk/month and 13.7 per cent were farmers.¹

TABLE 15

DATA 1045 FOR CHILD DISEASE TO HOSPITAL ADMISSION TO MOTHER'S STATE OF HEALTH

	Psychological factors in the family		Social indications		Purely medical indications	Total series
Healthy	129	(2.3 %)	427	(6.3 %)	6180 (91.4 %)	6706 (100 %)
Poor condition	9	(2.4 %)	42	(11.4 %)	319 (86.2 %)	370 (100 %)
Sick	4	(2.2 %)	25	(13.9 %)	151 (83.9 %)	180 (100 %)
Total	172	(2.4 %)	494	(6.8 %)	6650 (90.8 %)	7316 (100 %)
					Not reported	638
						7954
					Non-response rate	8.0 %

¹ 600 Fmk was at that time (1963-64) equivalent to 186 U.S. \$ and 1000 Fmk to 310 U.S. \$.

TABLE 11

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY LEGITIMACY OR ILLEGITIMACY

	Psychological factors in the family	Social indications	Purely medical indications	Total series
Legitimate children	170 (2.1 %)	442 (6.2 %)	6503 (91.1 %)	7115 (100 %)
Illegitimate children	6 (1.9 %)	77 (24.4 %)	233 (73.7 %)	316 (100 %)
Total	176 (2.4 %)	519 (7.0 %)	6736 (90.6 %)	7151 (100 %)
			Not reported	523
				7954
			Non-response rate	6.6 %

TABLE 12

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY ITS BIRTH ORDER AND BIRTH DATE

	Psychological factors in the family	Social indications	Purely medical indications	Total series
No siblings	1 (2.3 %)	183 (9.3 %)	1742 (88.4 %)	1970 (100 %)
Eldest	1 (2.2 %)	58 (5.4 %)	987 (92.4 %)	1069 (100 %)
2nd or 3rd child	80 (2.3 %)	209 (6.6 %)	2875 (90.9 %)	3164 (100 %)
4th or 5th child	28 (3.0 %)	53 (5.6 %)	863 (91.4 %)	944 (100 %)
6th to 16th child	2 (0.4 %)	27 (6.0 %)	424 (93.6 %)	453 (100 %)
Total	179 (2.1 %)	530 (7.0 %)	6891 (90.6 %)	7600 (100 %)
			Not reported	354
				7954
			Non-response rate	4.5 %

TABLE 13

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY MOTHER'S EMPLOYMENT OUTSIDE THE HOME

	Psychological factors in the family	Social indications	Purely medical indications	Total series
No gainful employment	107 (2.3 %)	198 (4.2 %)	4358 (93.5 %)	1663 (100 %)
Part-time employment	9 (2.6 %)	17 (4.9 %)	324 (92.5 %)	350 (100 %)
Full-time employment	33 (2.5 %)	275 (12.7 %)	1841 (84.8 %)	2171 (100 %)
Total	171 (2.4 %)	490 (6.8 %)	6253 (90.6 %)	7184 (100 %)
			Not reported	770
				7954
			Non-response rate	9.7 %

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents or foster parents of the child patients of the present study had a private car of their own.

Psychological factors affected the child's admission to hospital more often in those cases in which the family had a car of their own than in those in which the family had no car. The difference was significant ($\chi^2 = 9.41$, $p < 0.01$).

Additional social indications affected the admission more often if the family had no car. The difference was highly significant ($\chi^2 = 51.40$, $p < 0.001$).

Table 16.

OWNERSHIP OF A TV SET

42.3 per cent of the homes of the child patients in the present study had a TV set.

Psychological factors affected the child's admission to hospital more often when the family had a TV set than when there was no TV. The difference was highly significant ($\chi^2 = 16.83$, $p < 0.001$).

No significant difference existed in social indications between the TV owners and those with no TV. Table 17.

TYPE OF COMMUNE

Of the children of the present study, 22.3 per cent came from Helsinki and 28.7 per cent from other towns, making a total of 51.0 per cent for urban children.

6.6 per cent came from market boroughs and 42.2 per cent from typical rural districts. If the market boroughs are classified as rural district, 49.0 per cent of the children came from communes of rural type.

A comparison of the urban and rural children revealed that psychological factors affected the admission of urban children slightly more often than that of the rural children. The difference was almost significant ($\chi^2 = 5.31$, $p < 0.05$).

Social indications were also more frequent for the urban than for the rural children. The difference was highly significant ($\chi^2 = 91.66$, $p < 0.001$).

A comparison of the Helsinki children with all others (the other towns, market boroughs and the rural districts) revealed no significant difference in the frequency of the psychological indications, whereas additional social indications were more frequent for the Helsinki children than for those from other localities. The difference was highly significant ($\chi^2 = 14.58$, $p < 0.001$). Helsinki did not differ significantly from the other towns, whereas a significant difference emerged between towns and rural areas. Table 18.

Factors connected with hospital

SOUTH AND NORTH FINLAND

77.4 per cent of the children of the present study came from South Finland and 22.6 per cent from North Finland.

TABLE 17

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY THE OWNERSHIP OF A TV SET AT HOME

	Psychological factors in the family	Social indications	Purely medical indications	Total series
Television +	99 (8.3 %) ^{ab}	190 (6.3 %)	2739 (90.4 %)	3028 (100 %)
Television —	72 (1.7 %) ^a	303 (7.3 %)	3757 (91.0 %)	4132 (100 %)
Total	171 (2.4 %)	493 (6.9 %)	6496 (90.7 %)	7160 (100 %)
			Not reported	794
				7934
			Non-response rate	10.0 %

TABLE 15

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY AGGREGATE EARNINGS OF THE PARENTS

	Psychological factors in the family		Social indications		Purely medical indications	Total series
< 600 mk/month	47	{(17 %)}	273	{(97 %)}	2483 (88.6 %)	2805 (100 %)
600—1000 mk/month	47	{(2.2 %)}	126	{(5.9 %)}	1955 (91.9 %)	2128 (100 %)
> 1000 mk/month	50	{(4.6 %)}	48	{(4.4 %)}	985 (91.0 %)	1083 (100 %)
Farmer family	24	(2.5 %)	28	(2.9 %)	903 (94.6 %)	955 (100 %)
Total	168	(2.4 %)	475	(6.8 %)	6328 (90.8 %)	6971 (100 %)
					Not reported	983
						7934
					Non-response rate	12.2 %

Significance tests were carried out in three stages: 1 farmers vs nonfarmers; 2 < 600 mk/month vs. > 600 mk/month farmers excluded; 3 600—1000 mk/month vs. < 1000 mk/month farmers excluded.

Frequencies of psychological factors did not differ significantly between farmers and non-farmers. Social indications affected the admission of farmers' children less frequently than that of non-farmers' children. The difference was highly significant ($\chi^2 = 25.56$, $p < 0.001$).

In the income bracket of a maximum 600 mk/month psychological factors affected admission to hospital less frequently than in the income bracket of over 600 mk/month. The difference was highly significant ($\chi^2 = 11.03$, $p < 0.001$).

If parental income did not exceed 600 mk/month social indications affected admission more often than if the income exceeded 600 mk/month. The difference was highly significant ($\chi^2 = 39.88$, $p < 0.001$).

When the income brackets were classified as a maximum of 1000 mk/month and over 1000 mk/month, psychological factors affected admission to hospital in the higher income bracket more often than in the lower. The difference was highly significant ($\chi^2 = 17.53$, $p < 0.001$). Social indications affected the admission in the lower income bracket (maximum 1000 mk/month) more often than in the higher. The difference was highly significant ($\chi^2 = 42.48$, $p < 0.001$). Table 15.

TABLE 16

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TITLE OWNERSHIP OF A PRIVATE CAR

	Psychological factors in the family		Social indications		Purely medical indications	Total series
Private car +	73	(3.2 %)	82	(3.6 %)	2094 (93.2 %)	2249 (100 %)
Private car —	98	(2.0 %)	403	(8.3 %)	4362 (89.7 %)	4863 (100 %)
Total	171	(2.4 %)	485	(6.8 %)	6456 (90.8 %)	7112 (100 %)
					Not reported	842
						7934
					Non-response rate	10.6 %

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents or foster parents of the child patients of the present study had a private car of their own.

Psychological factors affected the child's admission to hospital more often in those cases in which the family had a car of their own than in those in which the family had no car. The difference was significant ($\chi^2 = 9.41$ $p < 0.01$).

Additional social indications affected the admission more often if the family had no car. The difference was highly significant ($\chi^2 = 51.40$ $p < 0.001$).

Table 16.

OWNERSHIP OF A TV SET

42.3 per cent of the homes of the child patients in the present study had a TV set.

Psychological factors affected the child's admission to hospital more often when the family had a TV set than when there was no TV. The difference was highly significant ($\chi^2 = 16.83$ $p < 0.001$).

No significant difference existed in social indications between the TV owners and those with no TV. Table 17.

TYPE BY COMMUNE

Of the children of the present study, 22.3 per cent came from Helsinki and 28.7 per cent from other towns, making a total of 51.0 per cent for urban children.

6.6 per cent came from market boroughs and 42.2 per cent from typical rural districts. If the market boroughs are classified as rural district, 49.0 per cent of the children came from communes of rural type.

A comparison of the urban and rural children revealed that psychological factors affected the admission of urban children slightly more often than that of the rural children. The difference was almost significant ($\chi^2 = 5.31$ $p < 0.05$).

Social indications were also more frequent for the urban than for the rural children. The difference was highly significant ($\chi^2 = 91.66$, $p < 0.001$).

A comparison of the Helsinki children with all others (the other towns, market boroughs and the rural districts) revealed no significant difference in the frequency of the psychological indications, whereas additional social indications were more frequent for the Helsinki children than for those from other localities. The difference was highly significant ($\chi^2 = 14.58$, $p < 0.001$). Helsinki did not differ significantly from the other towns, whereas a significant difference emerged between towns and rural areas. Table 18.

Factors connected with hospital

SOUTH AND NORTH FINLAND

77.4 per cent of the children of the present study came from South Finland and 22.6 per cent from North Finland.

TABLE 17

INDICATIONS FOR CHILD ADMITTED TO HOSPITAL BY THE OWNERSHIP OF A TV SET HOME

	Psychological factors in the family	Social indications	Purely medical indications	Total series
Television +	99 (3.3 %)	190 (6.3 %)	2739 (90.4 %)	3028 (100 %)
Television —	72 (1.7 %)	303 (7.3 %)	3757 (91.0 %)	4132 (100 %)
Total	171 (2.4 %)	493 (6.9 %)	6496 (90.7 %)	7160 (100 %)
			Not reported	794
				7934
			Non-response rate	10.0 %

TABLE 18
INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF DOMICILE

	Psychological factors in the family		Social indications		Purely medical indications	Total series
Helsinki	39	(2.3)	154	(9.1)	1,502 (88.6)	1695 (100)
Other cities	68	(3.1)	223	(10.2)	1889 (86.7)	2180 (100 %)
Market boroughs	15	(3.0)	4	(4.8)	462 (92.2 %)	510 (100 %)
Rural communes	57	(1.8)	129	(4.0)	3038 (94.2)	3224 (100)
Total	179	(2.4)	330	(7.0)	6891 (90.6)	7600 (100 %)
Not reported						354
						7954
Non-response rate						4.4

TABLE 19
INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL IN SOUTH AND NORTH FINLAND

	Psychological factors in the family		Social indications		Purely medical indications	Total series
South Finland	147	(5.5)	469	(8.1)	5156 (89.4)	5772 (100 %)
North Finland	8	(1.7)	44	(2.6 %)	1610 (94.7)	1682 (100 %)
Total	175	(3.3)	513	(6.9)	6766 (90.8)	7454 (100)
Not reported						500
						7954
Non-response rate						6.3

TABLE 20
INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF HOSPITAL

	Psychological factors in the family		Social indications		Purely medical indications	Total series
University teaching hospitals and Child- ren Castle, Hel- sinki	86	(3.9)	103	(4.8)	2013 (91.3)	2204 (100)
City Hospital of Hel- sinki	2	(0.2)	117	(9.6)	1104 (90.2)	1223 (100)
Hospitals with sever- al pediatricians	48	(2.0)	92	(3.8)	2309 (94.2)	2449 (100)
Hospitals with one pediatrician	43	(2.5 %)	216	(12.7 %)	1448 (84.8)	1707 (100)
Total	179	(2.4)	530	(7.0)	6874 (90.6)	7583 (100)
Not reported						371
						7954
Non-response rate						4.7 %

Psychological factors were associated with hospital admission more often in the South than in the North. The difference was almost significant ($\chi^2 = 4.04$ $p < 0.05$).

The social indications also contributed to admission more often in South than in North Finland. The difference was highly significant ($\chi^2 = 60.84$ $p < 0.001$) Table 19.

TYPE OF HOSPITAL

29.1 per cent of the patients of the present study had been admitted to hospitals of Type 1, 16.1 per cent to the City Hospital of Helsinki, 32.3 per cent to hospitals with several pediatricians and 22.5 per cent to hospitals with one pediatrician.

Significance tests have been carried out separately for every hospital type versus others.

Psychological indications were associated with admission to hospitals of Type 1 more often than with that to the other hospitals. The difference was highly significant ($\chi^2 = 31.10$, $p < 0.001$). In the City Hospital of Helsinki, psychological factors were associated less frequently than in the other hospital types. The difference was highly significant ($\chi^2 = 29.41$ $p < 0.001$).

Social indication affected admission to hospitals of Type 1 less often than that to the other hospitals. The difference was highly significant ($\chi^2 = 23.19$ $p < 0.001$). The admission to hospitals with several pediatricians was also associated with social factors less frequently than that to the other hospitals. The difference was significant ($\chi^2 = 8.36$ $p < 0.01$). Admission to hospitals with one pediatrician was associated with social factors more often than that to the other hospitals. The difference was highly significant ($\chi^2 = 107.60$ $p < 0.001$). The same was true of the City Hospital of Helsinki — that is to say social indications affected the admission more often than for the other types of hospitals. The difference was highly significant ($\chi^2 = 11.43$ $p < 0.001$) Table 20.

Indications for admission

When the effect of different factors on admissions for psychic diseases (= mental disorders) and for functional symptoms were compared, the first classification was purely medical vs. social and psychological indications. In the psychic diseases group, admissions for purely medical indications were fewer (2.5 per cent) than those for other indications (social indications 7.7 per cent and psychological indications 21.7 per cent). The difference was highly significant ($\chi^2 = 152.20$ $p < 0.001$). Admissions for functional symptoms were fewer on the basis of purely medical indications than medical combined with social and/or psychological contributory factors. The difference was highly significant ($\chi^2 = 19.77$ $p < 0.001$) Table 21.

Factors connected with the child

SEX

56.6 per cent of the present series of children were boys and 43.4 per cent were girls. In the psychic diseases group 66.5 per cent were boys and 33.5 per cent girls. In the functional symptoms group 54.8 per cent were boys and 45.2 per cent girls.

A higher percentage of boys than girls was admitted to hospital for psychic diseases. The difference was significant ($\chi^2 = 10.54$ $p < 0.01$).

No significant difference between boys and girls was noted in the frequency of functional symptoms. Table 22.

AGE

12.0 per cent of the present series of children were less than 1 month old, 21.6 per cent 1–11 months, 42.3 per cent pre-school age (1–6 years) and 23.7 per cent school age (7–15 years).

For the statistical test the children were divided into two groups: those up to

TABLE III
INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF DOWELCE

	Psychological factors in the family		Social indications		Purely medical indications	Total series
Helsinki	39	(25 %)	154	(91 %)	1502 (88.6 %)	1695 (100 %)
Other cities	68	(31 %)	223	(10.2 %)	1889 (86.7 %)	2180 (100 %)
Market boroughs	15	(3.0 %)	24	(4.8 %)	462 (92.2 %)	510 (100 %)
Rural communities	57	(1.8 %)	129	(4.0 %)	3038 (94.4 %)	3224 (100 %)
Total	179	(2.4 %)	530	(7.0 %)	6891 (90.6 %)	7600 (100 %)
Not reported						354
						7954
Non-response rate						4.4

TABLE 19
INDICATION FOR CHILD'S ADMISSION TO HOSPITAL IN SOUTH AND NORTH FINLAND

	Psychological factors in the family		Social indications		Purely medical indications	Total series
South Finland	147	(2.5 %)	469	(8.1 %)	5156 (89.4 %)	5772 (100 %)
North Finland	78	(1.7 %)	44	(2.6 %)	1610 (95.7 %)	1682 (100 %)
Total	175	(2.3 %)	513	(6.9 %)	6766 (90.8 %)	7454 (100 %)
Not reported						500
						7954
Non-response rate						6.3 %

TABLE 20
INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF HOSPITAL

	Psychological factors in the family		Social indications		Purely medical indications	Total series
University teaching hospitals and Child ren Castle Helsinki	86	(3.9 %)	105	(4.8 %)	2013 (91.3 %)	2204 (100 %)
City Hospital of Helsinki	2	(0.2 %)	117	(9.6 %)	1104 (90.2 %)	1223 (100 %)
Hospitals with several pediatricians	48	(2.0 %)	92	(3.8 %)	2309 (94.2 %)	2449 (100 %)
Hospitals with one pediatrician	43	(2.5 %)	216	(12.7 %)	1448 (84.8 %)	1707 (100 %)
Total	179	(2.4 %)	530	(7.0 %)	6874 (90.6 %)	7583 (100 %)
Not reported						371
						7954
Non-response rate						4.7

Psychological factors were associated with hospital admission more often in the South than in the North. The difference was almost significant ($\chi^2 = 4.04$ $p < 0.05$).

The social indications also contributed to admission more often in South than in North Finland. The difference was highly significant ($\chi^2 = 60.84$ $p < 0.001$) Table 19.

TYPE OF HOSPITAL

29.1 per cent of the patients of the present study had been admitted to hospitals of Type 1, 16.1 per cent to the City Hospital of Helsinki, 32.3 per cent to hospitals with several pediatricians and 22.5 per cent to hospitals with one pediatrician.

Significance tests have been carried out separately for every hospital type versus others.

Psychological indications were associated with admission to hospitals of Type 1 more often than with that to the other hospitals. The difference was highly significant ($\chi^2 = 31.10$, $p < 0.001$). In the City Hospital of Helsinki psychological factors were associated less frequently than in the other hospital types. The difference was highly significant ($\chi^2 = 29.41$ $p < 0.001$).

Social indications affected admission to hospitals of Type 1 less often than that to the other hospitals. The difference was highly significant ($\chi^2 = 23.19$ $p < 0.001$). The admission to hospitals with several pediatricians was also associated with social factors less frequently than that to the other hospitals. The difference was significant ($\chi^2 = 8.36$ $p < 0.01$). Admission to hospitals with one pediatrician was associated with social factors more often than that to the other hospitals. The difference was highly significant ($\chi^2 = 107.60$ $p < 0.001$). The same was true of the City Hospital of Helsinki — that is to say social indications affected the admission more often than for the other types of hospitals. The difference was highly significant ($\chi^2 = 14.43$ $p < 0.001$) Table 20.

Indications for admission

When the effect of different factors on admissions for psychic diseases (= mental disorders) and for functional symptoms were compared, the first classification was purely medical vs. social and psychological indications. In the psychic diseases group admissions for purely medical indications were fewer (2.5 per cent) than those for other indications (social indications 7.7 per cent and psychological indications 21.7 per cent). The difference was highly significant ($\chi^2 = 152.20$, $p < 0.001$). Admissions for functional symptoms were fewer on the basis of purely medical indications than medical combined with social and/or psychological contributory factors. The difference was highly significant ($\chi^2 = 19.77$ $p < 0.001$) Table 21.

Factors connected with the child

SEX

56.6 per cent of the present series of children were boys and 43.4 per cent were girls. In the psychic diseases group 66.5 per cent were boys and 33.5 per cent girls. In the functional symptoms group 54.8 per cent were boys and 45.2 per cent girls.

A higher percentage of boys than girls was admitted to hospital for psychic diseases. The difference was significant ($\chi^2 = 10.54$ $p < 0.01$).

No significant difference between boys and girls was noted in the frequency of functional symptoms. Table 22.

AGE

12.0 per cent of the present series of children were less than 1 month old, 21.6 per cent 1–11 months, 42.3 per cent pre-school age (1–6 years) and 23.7 per cent school age (7–15 years).

For the statistical test the children were divided into two groups: those up to

TABLE 21
INDICATIONS FOR HOSPITAL ADMISSION OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total
Purely medical	182 (2.5 %)	507 (7.1 %)	6157 (90.4 %)	7146 (100 %)
Partly or decisively social	43 (7.7 %)	31 (5.6 %)	483 (86. 7%)	557 (100 %)
Partly or decisively due to psychological factors in the family	40 (21.7 %)	50 (27.2 %)	94 (51.1 %)	184 (100 %)
T tal	265 (3.4 %)	588 (7.4 %)	7034 (89.2 %)	7887 (100 %)
			Not reported	67
				7954
			Non-response rate	0.3 %

TABLE 22
SEX DISTRIBUTION

	Mental disorders	Functional symptoms	Other diseases	Total series
Girls	88 (2.6 %)	263 (7.7 %)	3080 (89.7 %)	3433 (100.0 %)
Boys	175 (3.9 %)	321 (7.2 %)	3980 (88.9 %)	4476 (100.0 %)
Total	263 (3.3 %)	586 (7.4 %)	7060 (89.3 %)	7909 (100.0 %)
			Not reported	45
				7954
			Non-response rate	0.6 %

TABLE 23
AGE OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total series
Under 1 month	2 (0.2 %)	57 (6.1 %)	882 (93.7 %)	941 (100.0 %)
1—11 months	5 (0.3 %)	77 (4.6 %)	1606 (95.1 %)	1688 (100.0 %)
1—6 yrs	118 (3.5 %)	230 (6.9 %)	2987 (89.6 %)	3335 (100.0 %)
7—15 yrs	139 (7.5 %)	214 (11.6 %)	1497 (80.9 %)	1850 (100.0 %)
Total	264 (3.4 %)	578 (7.4 %)	6972 (89.2 %)	7814 (100.0 %)
			Not reported	140
				7954
			Non-response rate	1.8 %

11 months, and those of one or more than one year

Psychic diseases were the main diagnosis for fewer infants (1—11 months) than for children of 1—15 years. The difference was highly significant ($\chi^2 = 116.13$ $p < 0.001$). The percentage of school age children (7—15 years) was highest, 7.5 per cent.

Admissions for functional symptoms of children aged more than 1 year were more frequent than those of infants. The difference was highly significant ($\chi^2 = 30.09$ $p < 0.001$). In the admissions for functional symptoms also, the largest individual age group was that of 7—15 years (11.6 per cent) even though these diagnoses occurred among infants under 1 month (6.1 per cent) whereas psychic diseases were very infrequent (0.2 per cent) in this age group.

There were more mental disorders in the age group of 7—15 years than under 7 years old. The difference was highly significant ($\chi^2 = 139.6$, $p < 0.001$). In the functional symptoms group there were also more children between 7 and 15 years than under 7 years. The difference was highly significant ($\chi^2 = 72.8$, $p < 0.001$). Table 23

LEGITIMACY OF THE CHILD

4.3 per cent of the children of the present series were born out of wedlock

while 95.7 per cent had parents who were married.

A comparison of the percentages of illegitimate and legitimate children in the admissions for psychic diseases and those for functional symptoms revealed no significant differences. In other words, admissions of illegitimate children for psychic diseases or functional symptoms were no more frequent or infrequent than those of legitimate children.

SENIORITY AMONG SIBLINGS

25.9 per cent of the present series of children were only children of their families, 14.1 per cent were eldest children, while 60 per cent were second, third etc. eldest.

Admissions for psychic diseases less frequently concerned the only child than one of several siblings. The difference was highly significant ($\chi^2 = 56.92$ $p < 0.001$). The same was true of admissions for functional symptoms. The difference was highly significant ($\chi^2 = 48.93$ $p < 0.001$).

From testing the eldest child against the others (second etc. eldest and the only child) it was found that eldest children were admitted for psychic symptoms more often than other children. The difference was almost significant ($\chi^2 = 5.37$ $p < 0.001$). In the functional symptoms

TABLE 24

SENIORITY OF THE CHILD AMONG SIBLINGS

	Mental disorders		Functional symptoms		Other diseases		Total series
Only child	43	(2.1)	147	(7.2)	1661	(90.7)	2051 (100.0)
Eldest	56	(3.0)	221	(8.3)	965	(86.7)	1113 (100.0)*
Second eldest etc.	166	(3.3)	249	(7.4)	4226	(89.1)	4741 (100.0)
Total	265	(3.4)	368	(7.4)	7052	(89.2)	7903 (100.0)
Not reported							49
							7954
Non-response rate							0.6 %

TABLE 21
INDICATIONS FOR HOSPITAL ADMISSION OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total
Purely medical	182 (2.3 %)*	507 (7.1 %)	6457 (90.4 %)	7146 (100 %)
Partly or decisively social	43 (7.7 %)	31 (5.6 %)	483 (86.7 %)	557 (100 %)
Partly or decisively due to psychological factors in the family	40 (21.7 %)	50 (27.2 %)	91 (51.1 %)	181 (100 %)
Total	265 (3.4 %)	588 (7.4 %)	7034 (89.2 %)	7887 (100 %)
			Not reported	67
				7954
			Non-response rate	0.3 %

TABLE 22
SEX DISTRIBUTION

	Mental disorders	Functional symptoms	Other diseases	Total series
Girls	88 (2.6 %)	263 (7.7 %)	3080 (89.7 %)	3133 (100.0 %)
Boys	175 (3.9 %)	321 (7.2 %)	3980 (88.9 %)	4476 (100.0 %)
Total	263 (3.3 %)	586 (7.4 %)	7060 (89.3 %)	7909 (100.0 %)
			Not reported	45
				7954
			Non-response rate	0.6 %

TABLE 23
AGE OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total series
Under 1 month	2 (0.2 %)	57 (6.1 %)	882 (93.7 %)	911 (100.0 %)
1—11 months	5 (0.3 %)	77 (4.6 %)	1608 (95.1 %)	1688 (100.0 %)
1—6 yrs	118 (3.5 %)	230 (6.9 %)	2987 (89.6 %)	3335 (100.0 %)
7—15 yrs	159 (7.5 %)	214 (11.6 %)	1497 (80.9 %)	1850 (100.0 %)
Total	264 (3.4 %)	578 (7.4 %)	6972 (89.2 %)	7814 (100.0 %)
			Not reported	140
				7954
			Non-response rate	1.8 %

group the difference between the eldest and the other children was not significant Table 24

Factors connected with the family and home

FATHER'S OCCUPATIONAL STATUS

49.4 per cent of the fathers of the present series of children were workers while the remainder belonged to groups shown in Table 25

Frequencies of psychic diseases and functional symptoms did not differ between the workers and the others

EDUCATIONAL LEVEL OF FATHER

80.0 per cent of the fathers of the present series of children had only passed through the primary school 14.2 per cent had matriculated 5.8 per cent had an academic degree.

For the statistical test the fathers were divided into those with primary school education and others

Admissions for psychic diseases or functional symptoms were not fewer or more numerous among children of fathers with primary school than among those with more educated fathers

When fathers with an academic degree

were tested against others there were more mental disorders in children of academic fathers than in children of other fathers. The difference was almost significant ($\chi^2 = 5.6$ $p < 0.05$) Table 26

FATHER'S MARITAL STATUS

90.2 per cent of the fathers of the present series of children were married 4.1 per cent were unmarried widowed or divorced and 5.7 per cent dead or not known

For the statistical test the children of unmarried widowed or divorced fathers and the children whose father was dead or whose father's marital status was unknown were added together. This group was tested against the children of married fathers

Admissions for psychic diseases of the children of single fathers were more frequent than of married fathers. The difference was highly significant ($\chi^2 = 16.73$ $p < 0.001$). Since the percentages for married fathers (3.0 per cent) and dead or unknown fathers (2.9 per cent) were of the same magnitude the difference is mainly derived from the share of the solitary (unmarried widowed or divorced) fathers (10.2 per cent)

Admissions for functional symptoms revealed no significant difference between these two groups of fathers Table 27

TABLE 2

FATHER'S OCCUPATION TITLES

	Mental disorders	Functional symptoms	Other diseases	Total
Worker	137 (33.5 %)	202 (72.2 %)	3511 (89.3 %)	3750 (100 %)
Self-employed	53 (3.5 %)	120 (7.8 %)	1561 (88.7 %)	1734 (100 %)
Manager executive	52 (2.9 %)	127 (7.2 %)	1588 (89.9 %)	1767 (100 %)
Assisting family member	0	1 (14.3 %)	6 (8.7 %)	7 (100 %)
Independent without occupation student inmate of an institution, dead or not known	3 (3.2 %)	58 (8.1 %)	635 (88.7 %)	716 (100 %)
Total	265 (53.3 %)	388 (74.4 %)	7101 (89.3 %)	7954 (100 %)

TABLE 26
ATERNAL EDUCATIONAL LEVEL

	Mental disorders	Functional symptoms	Other diseases	Total series
1-3	191 (3.4 %)	423 (7.4 %)	4064 (89.2 %)	5698 (100 %)
4-7	19 (1.9 %)	79 (7.8 %)	919 (90.3 %)	1017 (100 %)
8	22 (3.4 %)	34 (8.3 %)	355 (86.3 %)	411 (100 %)
Total	232 (3.3 %)	536 (7.5 %)	6358 (89.2 %)	7126 (100 %)
			Not reported	828
				7954
			Non-response rate	10.4

- 1-3 = primary school
 4 = secondary school, lower forms
 5 = secondary school, (n. forms (middle school)
 6 = secondary school, more than five forms but no matriculation
 7 = matriculation but no university or other degree
 8 = university or other degree

TABLE 27
THEIR MARITAL STATUS

	Mental disorders	Functional symptoms	Other diseases	Total series
Married	219 (3.0 %)	536 (7.5 %)	6418 (89.5 %)	7173 (100 %)
Subsary	33 (10.2 %)	25 (7.7 %)	267 (82.1 %)	325 (100 %)
Dead or not know	13 (2.9 %)	27 (5.9 %)	416 (91.2 %)	456 (100 %)
Total	265 (3.3 %)	588 (7.4 %)	7101 (89.3 %)	7954 (100 %)

TABLE 28
THEIR AGGREGATE MONTHLY EARNINGS THE ARE TS

	Mental disorders	Functional symptoms	Other diseases	Total series
≤ 1000 mk	134 (3.0 %)	382 (7.4 %)	4631 (89.6 %)	5167 (100.0 %)
1000 mk	47 (4.2 %)	96 (8.6 %)	977 (87.2 %)	1120 (100.0 %)
Farmer family	39 (3.9 %)	68 (6.7 %)	902 (89.4 %)	1009 (100.0 %)
Total	240 (3.3 %)	546 (7.3 %)	6510 (89.2 %)	7296 (100.0 %)
			Not reported	658
				7954
			Non-response rate	8.3

group the difference between the eldest and the other children was not significant. Table 24

Factors connected with the family and home

FATHER'S OCCUPATIONAL STATUS

49.4 per cent of the fathers of the present series of children were workers, while the remainder belonged to groups shown in Table 25

Frequencies of psychic diseases and functional symptoms did not differ between the workers and the others

EDUCATIONAL LEVEL OF FATHER

80.0 per cent of the fathers of the present series of children had only passed through the primary school 14.2 per cent had matriculated 5.8 per cent had an academic degree

For the statistical test the fathers were divided into those with primary school education and others.

Admissions for psychic diseases or functional symptoms were not fewer or more numerous among children of fathers with primary school than among those with more educated fathers

When fathers with an academic degree

were tested against others there were more mental disorders in children of academic fathers than in children of other fathers. The difference was almost significant ($\chi^2 = 5.6$ $p < 0.05$) Table 26

FATHER'S MARITAL STATUS

90.2 per cent of the fathers of the present series of children were married, 4.1 per cent were unmarried widowed or divorced and 5.7 per cent dead or not known

For the statistical test the children of unmarried widowed or divorced fathers and the children whose father was dead or whose father's marital status was unknown were added together. This group was tested against the children of married fathers.

Admissions for psychic diseases of the children of single fathers were more frequent than of married fathers. The difference was highly significant ($\chi^2 = 16.73$ $p < 0.001$). Since the percentages for married fathers (3.0 per cent) and dead or unknown fathers (2.9 per cent) were of the same magnitude the difference is mainly derived from the share of the solitary (unmarried widowed or divorced) fathers (10.2 per cent)

Admissions for functional symptoms revealed no significant difference between these two groups of fathers Table 27

TABLE 25

FATHER OCCUPATIONAL STATUS

	Mental disorders	Functional symptoms	Other diseases	Total
Worker	137 (3.5 %)	282 (7.2)	3511 (89.3)	3930 (100)
Self-employed	53 (3.3 %)	120 (7.8)	1361 (88.7)	1534 (100)
Manager executive	52 (2.9 %)	127 (7.2)	1588 (89.9)	1767 (100)
Assisting family member	0	1 (14.3)	6 (85.7)	7 (100)
Independent without occupation, student, inmate of an institution, dead or not known	23 (3.2 %)	58 (8.1)	635 (88.7)	716 (100)
Total	265 (3.3 %)	588 (7.4 %)	7101 (89.3)	7954 (100)

TABLE 26
RURAL EDUCATIONAL LEVEL

	Mental disorders	Functional symptoms	Other diseases	Total series
1-3	191 (3.4 %)	423 (7.4 %)	508 (89.2 %)	569 (100 %)
4-7	19 (1.9 %)	79 (7.8 %)	919 (90.3 %)	1017 (100 %)
8	22 (3.4 %)	54 (8.3 %)	355 (86.3 %)	411 (100 %)
Total	232 (3.3 %)	556 (7.5 %)	63.8 (89.2 %)	7126 (100 %)
			Not reported	828
				7954
			Non-response rate	10.4

- 1-3 = primary school
 4 = secondary school, lower forms
 5 = secondary school, 7th forms (paldie school)
 6 = secondary school, more than five forms but no matriculation
 7 = matriculation but no university or other degree
 8 = university or other degree

TABLE 27
SEX MARITAL BY AGE

	Mental disorders	Functional symptoms	Other diseases	Total series
Married	219 (3.0 %)	356 (7.5 %)	6418 (89.5 %)	7173 (100 %)
Single	33 (10.2 %)	23 (7.7 %)	267 (82.1 %)	325 (100 %)
Dead or not know	13 (2.9 %)	27 (5.9 %)	416 (91.2 %)	456 (100 %)
Total	265 (3.3 %)	588 (7.4 %)	7101 (89.3 %)	7954 (100 %)

TABLE 28
THE AGGREGATE MONTHLY EARNINGS THE AGGREGATE

	Mental disorders	Functional symptoms	Other diseases	Total series
≤ 1000 mk	154 (3.0 %)	382 (7.4 %)	4631 (89.6 %)	5167 (100.0 %)
1000 mk	47 (4.2 %)	96 (8.6 %)	977 (87.2 %)	1120 (100.0 %)
Farmer family	39 (3.9 %)	68 (6.7 %)	902 (89.4 %)	1009 (100.0 %)
Total	240 (3.3 %)	546 (7.5 %)	6510 (89.2 %)	7296 (100.0 %)
			Not reported	658
				7954
			Non-response rate	8.3

76.6 per cent of the parents of the present series of children had monthly income of maximum 1000 ml. 15.4 per cent over 1000 ml. and 5.6 per cent were unknown.

The testing was carried out in two stages. In the first, frequency of mental disorders in children from farming families was compared with that in children from non-farming families. The difference was not significant nor was it for functional symptoms.

In the second test children from farming families were excluded and the frequency of mental disorders and non-mental symptoms were compared in the two urban areas. Mental disorders in primary school children were more common in children from non-farming families

than lower 50 per cent income families. The difference was almost significant $t = 4.01$ $p < 0.05$ Table 2.

TABLE OF INHABITANTS PER ROOM IN THE FAMILY

40.1 per cent of the present series of children lived in a person per room, 22.1 per cent in families with a living density of 2 persons per room, and 7.3 per cent in families with a living density of 3 persons per room. (1.2 per cent = 10 inhabitants per room).

The group with one inhabitant per room was compared in the families with the families with a living density of more than one per room.

In the psychotic diseases group the difference between the two living

TABLE 1

MENTAL DISORDERS IN FARMING AND NON-FARMING FAMILIES

Area	Age	Sex	Disorder	Frequency	Percentage	Total
Farming	1-10	M	Psychotic	1	100	1
Farming	1-10	F	Psychotic	1	100	1
Non-farming	1-10	M	Psychotic	1	100	1
Non-farming	1-10	F	Psychotic	1	100	1
Total						4

Psychotic

Non-psychotic

TABLE 2

MENTAL DISORDERS IN FARMING AND NON-FARMING FAMILIES

Area	Age	Sex	Disorder	Frequency	Percentage	Total
Farming	1-10	M	Psychotic	1	100	1
Farming	1-10	F	Psychotic	1	100	1
Non-farming	1-10	M	Psychotic	1	100	1
Non-farming	1-10	F	Psychotic	1	100	1
Total						4

Psychotic

groups were not significant. The functional symptoms group contained more children of families with one inhabitant per room than of families with more than one inhabitant per room. The difference was almost significant ($\chi^2 = 4.99$ $p < 0.05$) Table 29

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents of the present series of children owned a private car while 68.4 per cent did not.

A comparison between car owners and non-owners revealed no significant differences in admissions for psychic diseases or in admissions for functional symptoms.

TELEVISION SET AT HOME

42.2 per cent of the homes of the present series of children had TV

Admissions for psychic diseases of children from families with TV were more frequent than those of children from families without TV. The difference was almost significant ($\chi^2 = 5.52$, $p < 0.05$)

In the functional symptoms group a similar difference was noted: children with TV at home were admitted more frequently than those who had no TV at home. The difference was almost significant ($\chi = 5.78$, $p < 0.05$) Table 30

OWNERSHIP OF A SUMMER COTTAGE

9.8 per cent of the parents of the present series of children had a summer cottage

Children of families with a summer cottage were admitted more frequently for psychic diseases than those of families without summer cottage. The difference was almost significant ($\chi^2 = 5.39$ $p < 0.05$)

The functional symptoms group revealed a similar difference: children of families with summer cottage were admitted more frequently than those of families without summer cottage. The difference was highly significant ($\chi^2 = 10.97$ $p < 0.001$) Table 31

DISTANCE BETWEEN CHILD'S HOME AND PHYSICIAN'S OFFICE

46.5 per cent of the present series of children lived at a maximum distance of 1 km from the physician's office, 16.2 per cent at 2—3 km, 17.7 per cent at 4—10 km and 19.6 per cent at more than 10 km distance.

Testing was carried out in two stages: 1 less than 1 km vs. more than 1 km, 2 less than 10 km vs. more than 10 km.

No significant differences were found between these groups in either psychic diseases or functional symptoms.

DISTANCE BETWEEN HOME AND HOSPITAL

46.2 per cent of the present series of children lived at a maximum distance of 10 km from the hospital, 38.3 per cent at 11—100 km, and 15.5 per cent over 100 km.

The testing was carried out in two stages: 1 maximum 10 km vs. more than

TABLE 31

OWNERSHIP OF A SUMMER COTTAGE

	Mental disorders		Functional symptoms		Other diseases		Total series	
Without cottage	33	4.9	76	10.6	608	84.5	719	(100.0)
With cottage	209	3.2	419	(71.2)	5945	(89.7)	6621	(100.0)
Total	244	3.3	495	(74.4)	6553	(89.3)	7340	(100.0)
Not reported							614	
							7954	
Non-response rate							7.7	

AGGREGATE INCOME

70.8 per cent of the parents of the present series of children had monthly incomes of maximum 1000 mk, 15.4 per cent over 1000 mk, and 13.8 per cent were farmers.

The testing was carried out in two stages. In the first, frequency of mental disorders in children from farming families was compared with that in children from non farming families. The difference was not significant nor was it for functional symptoms.

In the second test children from farming families were excluded and the frequencies of mental disorders (and functional symptoms) were compared in the two income classes. Mental disorders (as primary diagnoses) were more prevalent in children from upper (4.2 per cent)

than lower (3.0 per cent) income families. The difference was almost significant ($\chi^2 = 4.01$ $p < 0.05$) Table 28

NUMBER OF INHABITANTS PER ROOM IN THE FAMILY

40.1 per cent of the homes of the present series of children housed one person per room. 32.1 per cent were families with a living density of 2-3 persons per room and 7.3 per cent were families with a living density of 4-6 persons per room. 0.5 per cent had over 6 inhabitants per room.

The group with one inhabitant per room was compared in the statistical test with the families with a living density of more than one per room.

In the psychiatric group the differences between these two living density

TABLE 29
NUMBER OF INHABITANTS PER ROOM IN THE FAMILY

	Mental disorders	Functional symptoms	Other diseases	Total series
1 person	99 (3.4)	24 (8.3)	2596 (88.3)	2940 (100)
2-3 persons	127 (3.3)	254 (6.7)	3434 (90.0)	3815 (100)
4-6 persons	13 (2.4)	11 (8.2)	182 (89.4)	339 (100)
Over 6 persons	2 (0.9)	3 (11.7)	27 (79.4)	34 (100)
Total	241 (3.3)	348 (7.5)	6539 (89.2)	7328 (100)
			Not reported	626
				7954
			No response	74

TABLE 30
TELEVISION

	Mental disorders	Functional symptoms	Other diseases	Total series
Television	124 (4.0)	262 (8.3)	755 (87.7)	3141 (100.0)
Television —	126 (2.9)	294 (6.8)	3881 (90.3)	4301 (100.0)
Total	250 (3.3)	556 (7.5)	6639 (89.2)	7445 (100.0)
			Not reported	509
				7954
			No response	64

groups were not significant. The functional symptoms group contained more children of families with one inhabitant per room than of families with more than one inhabitant per room. The difference was almost significant ($\chi^2 = 4.99$ $p < 0.05$) Table 29

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents of the present series of children owned a private car while 68.4 per cent did not.

A comparison between car owners and non-owners revealed no significant differences in admissions for psychic diseases or in admissions for functional symptoms.

TELEVISION SET AT HOME

42.2 per cent of the homes of the present series of children had TV

Admissions for psychic diseases of children from families with TV were more frequent than those of children from families without TV. The difference was almost significant ($\chi^2 = 3.52$, $p < 0.05$)

In the functional symptoms group a similar difference was noted: children with TV at home were admitted more frequently than those who had no TV at home. The difference was almost significant ($\chi^2 = 5.78$ $p < 0.05$) Table 30

OWNERSHIP OF A SUMMER COTTAGE

9.8 per cent of the parents of the present series of children had a summer cottage.

Children of families with a summer cottage were admitted more frequently for psychic diseases than those of families without summer cottage. The difference was almost significant ($\chi^2 = 5.39$ $p < 0.05$)

The functional symptoms group revealed a similar difference: children of families with summer cottage were admitted more frequently than those of families without summer cottage. The difference was highly significant ($\chi^2 = 10.97$ $p < 0.001$) Table 31

DISTANCE BETWEEN CHILD'S HOME AND PHYSICIAN'S OFFICE

46.5 per cent of the present series of children lived at a maximum distance of 1 km from the physician's office, 16.2 per cent at 2-3 km, 17.7 per cent at 4-10 km, and 19.6 per cent at more than 10 km distance.

Testing was carried out in two stages: 1. less than 1 km vs. more than 1 km, 2. less than 10 km vs. more than 10 km.

No significant differences were found between these groups in either psychic diseases or functional symptoms.

DISTANCE BETWEEN HOME AND HOSPITAL

46.2 per cent of the present series of children lived at a maximum distance of 10 km from the hospital, 38.3 per cent at 11-100 km, and 15.5 per cent over 100 km.

The testing was carried out in two stages: 1. maximum 10 km vs. more than

TABLE 31

OWNERSHIP OF A SUMMER COTTAGE

	Mental disorders	Functional symptoms	Other diseases	Total cases
Without a lake	33 4.9	76 10.6 ***	608 (84.5)	719 (100.0)
With a lake	209 3.2	469 (71.2) **	943 (89.7)	621 (100.0)
Total	44 3.3	545 (74.4)	6551 (89.3)	7340 (100.0)
			Not reported	614
				7954
			Non-responsive case	77

TABLE 3

DISTANCE OF CHILD & HOME FROM HOSPITAL

	Mental disorders	Functional symptoms	Other diseases	Total series
≤ 10 km	72 { (2.1)	253 { (7.2)	3161 (90.7 %)	3486 (100.0 %)
11—100 km	114 { (3.9)	186 { (6.4 %)	2396 (89.7 %)	2896 (100.0 %)
> 100 km	71 (6.0)	121 (10.3 %)	982 (83.7 %)	1174 (100.0 %)
Total	257 (3.4 %)	560 (7.4 %)	6739 (89.2 %)	7556 (100.0 %)
			Not reported	998
				7934
			Non response rate	5.0

10 km 2 maximum 100 km vs. more than 100 km

Admissions for psychic diseases of children living at a maximum 10 km distance from the hospital were fewer than those of children more than 10 km distant from hospital. The difference was highly significant ($\chi^2 = 34.40$ $p < 0.001$). In admissions for functional symptoms the differences were not significant between those living at maximum 10 km and those living more than 10 km distant from hospital.

The psychic diseases group contained a larger number of children living more than 100 km distant from hospital than those living at a maximum 100 km distance. The difference was highly significant ($\chi^2 = 28.68$ $p < 0.001$). The functional symptoms group also contained a larger number of children living at a distance of more than 100 km from hospital. The difference was highly significant ($\chi^2 = 16.48$ $p < 0.001$). Table 32

TYPE OF RESIDENTIAL COMMUNE

21.7 per cent of the present series of children came from Helsinki, 29.4 per cent from the other towns, 6.5 per cent from market boroughs and 42.4 per cent from rural districts.

For statistical testing the children from Helsinki and other towns were combined (= urban 51.1 per cent) and those from market boroughs and rural districts were also combined (= rural 48.9 per cent).

No significant differences were noted in the frequency of admissions for psychic diseases or functional symptoms between urban and rural children.

When the Helsinki children were tested vs. all others, there was no significant difference between these groups in the frequency of admissions for psychic diseases. In admissions for functional symptoms, more children from Helsinki than from other localities were among the admitted. The difference was almost significant ($\chi^2 = 4.78$ $p < 0.051$). Table 33

Factors connected with the hospital

SOUTH OR NORTH FINLAND

18.2 per cent of the present series of children came from North Finland (for definition see p. 19 above) and 81.8 per cent from South Finland.

The numbers of children coming from North and South Finland revealed no significant differences in admissions for psychic diseases. In other words, the number of children admitted for psychic diseases from North Finland was significantly neither higher nor lower than that admitted from South Finland.

Admissions for functional symptoms of children from North Finland were more numerous than from South Finland. The difference was highly significant ($\chi^2 = 53.78$ $p < 0.001$). Table 34

TABLE 33
TYPE OF CHILD DOMICILE

	Mental disorders	Functional symptoms	Other diseases	Total series
Helsinki	49 (2.9 %)	149 (8.6 %)	1525 (88.5 %)	1723 (100.0 %)
Other city	73 (3.1 %)	168 (7.2 %)	2094 (89.7 %)	2335 (100.0 %)
Other urban district	18 (3.5 %)	32 (6.2 %)	466 (90.3 %)	516 (100.0 %)
Rural district	125 (3.7 %)	239 (7.1 %)	3010 (89.2 %)	3374 (100.0 %)
Total	265 (3.3 %)	588 (7.4 %)	7095 (89.3 %)	7948 (100.0 %)

TABLE 34
SOUTH FINLAND AND NORTH FINLAND

	Mental disorders	Functional symptoms	Other diseases	Total series
South Finland	214 (3.4 %)	404 (6.5 %)**	5759 (90.3 %)	6377 (100.0 %)
North Finland	46 (3.2 %)	170 (12.0 %)	1204 (84.8 %)	1420 (100.0 %)
Total	260 (3.3 %)	574 (7.4 %)	6963 (89.3 %)	7797 (100.0 %)
			Not reported	157
				7954
			Non-response rate	2.0 %

TABLE 35
DISTRIBUTION OF CASES ACCORDING TO TYPE OF HOSPITAL

	Mental disorders	Functional symptoms	Other diseases	Total series
University teaching hospitals and Children's Centre Helsinki	154 (6.9 %)	187 (8.3 %)	1899 (84.8 %)	2240 (100.0 %)
City Hospital of Helsinki/Aurora	15 (1.2 %)*	103 (8.4 %)	1110 (90.4 %)	1228 (100.0 %)
Hospitals with several pediatricians	67 (2.5 %)	208 (7.7 %)	2443 (89.8 %)	2718 (100.0 %)
Hospitals with one pediatrician	29 (1.7 %)**	88 (5.2 %)	1574 (93.1 %)	1691 (100.0 %)
Total	265 (3.4 %)	586 (7.4 %)	7026 (89.2 %)	7877 (100.0 %)
			Not reported	76
				7953
			Non-response rate	1.0 %

HOSPITAL TYPE

28.4 per cent of the present series of children had been treated at university central hospitals and the Children's Castle of Helsinki (= Type 1) 15.6 per cent in City Hospital of Helsinki 34.5 per cent in hospitals with two or more pediatricians and 21.5 per cent in units with one pediatrician.

Each hospital type was tested against the others.

Admissions for psychic diseases to hospitals of Type 1 were more frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 117.20$, $p < 0.001$).

Admissions for psychic diseases to City Hospital of Helsinki (= Type 2) were less frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 19.77$, $p < 0.001$).

Admissions for psychic diseases to hospitals with two or more pediatricians were less frequent than to the other hospitals. The difference was significant ($\chi^2 = 9.92$, $p < 0.01$).

Admissions for psychic diseases to hospitals with one pediatrician were also less frequent than admissions to the other hospitals. The difference was highly significant ($\chi^2 = 17.37$, $p < 0.001$).

Only one type of hospital was significantly different from the others in the frequency of admissions for functional symptoms: units with one pediatrician had a lower frequency than the other hospitals. The difference was highly significant ($\chi^2 = 15.35$, $p < 0.001$).
Table 35

ADMISSION DELAY

87.2 per cent of the present series of children did not have to wait at all for admission; 4.3 per cent waited for a maximum of one week; 3.4 per cent for 8–30 days; and 5.1 per cent for more than a month.

Table 37 gives the percentages of admission delays by diagnostic groups. While only 5.1 per cent of the total series had to wait for admission for more than a month, the corresponding figure among admissions for psychic diseases was 31.3

per cent. While 3.4 per cent of the total series waited for 8–30 days, the figure among admissions for psychic diseases was 15.1 per cent.

When those with no delay in admission were tested against all others, it was found that there were fewer undelayed admissions in the psychic diseases group. The difference was highly significant ($\chi^2 = 382.57$, $p < 0.001$).

A similar difference was seen in admissions for functional diseases: children were admitted less frequently without delay than after a period of queuing up. The difference was highly significant ($\chi^2 = 17.11$, $p < 0.001$).

When the group of children who had had to wait for a maximum of one month was tested against that with a waiting period exceeding one month, it was found that children had had to wait for admission for psychic diseases more frequently for more than a month than for a month. The difference was highly significant ($\chi^2 = 385.94$, $p < 0.001$).

Children with functional symptoms had had to wait for more than a month less frequently than for a maximum of a month. The difference was highly significant ($\chi^2 = 275.39$, $p < 0.001$). Table 36

POSSIBILITIES OF AN EARLIER DISCHARGE

For purely medical, therapeutic reasons, 90.1 per cent of the present series of children could not have been discharged earlier, while 9.9 per cent had some factors prolonging their stay in hospital. The biggest group among these factors was difficult home conditions (4.5 per cent of the total series).

A larger proportion of the children kept in hospital for not purely medical therapy had been admitted for psychic diseases than of the children with no additional indications. The difference was highly significant ($\chi^2 = 13.58$, $p < 0.001$).

The percentages of admissions for functional symptoms did not differ significantly between these two groups. But in the group of children who had to wait for examination, the percentage of functional symptoms (26.2 per cent) was relatively high. Table 38

TABLE 36

HOW LONG IN THE CHILD HAVE TO WAIT FOR DISMISS ?

	Mental disorders	Functional symptoms	Other diseases	Total series
Not at all	176 { (1.8 %)	480 { (6.9 %) **	6390 (91.3 %)	6936 (100.0 %)
≤ 7 day	16 { (4.7 %)	45 { (13.1 %)	282 (82.2 %)	343 (100.0 %)
8-30 day	40 { (14.8 %)	29 { (10.7 %)	202 (74.5 %)	271 (100.0 %)
1 month	83 (20.5 %)	34 (8.4 %)	287 (71.1 %)	404 (100.0 %)
Total	265 (9.3 %)	588 (7.4 %)	7101 (89.3 %)	7954 (100.0 %)

TABLE 37

THE CHILD WAITING TIME (= ADMISSIO DELA) IN DIFFERENT DIAGNOSTIC GROUPS

	Mental disorders	Functional symptoms	Other diseases	Total series
		%		%
Not at all	47.6	81.6	89.2	87.2
≤ 7 days	6.0	7.7	4.0	4.5
8-30 day	13.1	1.9	2.8	3.4
1 month	11.3	1.8	4.0	5.1
Total	100.0	100.0	100.0	100.0

TABLE 38

DO THE CHILD BE BEEN DISMISSED EARLIER

	Mental disorders	Functional symptoms	Other diseases	Total series
N	148 (2.3)	472 (7.4)	5743 (90.3)	6363 (100.0)
Yes, if the child had been better	13 (1.1)	6 (1.9)	293 (94.0)	318 (100.0)
Yes, if the child's home had been nearer hospital	3 (4.0)	3 (4.0)	68 (92.0)	74 (100.0)
Yes, if the child had not acquired an infection so as the hospital	3 (4.2)	2 (2.8)	67 (93.0)	72 (100.0)
Yes, if there had been no admission period before examination	7 (6.8)	29 (28.2)	67 (83.0)	103 (100.0)
Yes, if certain other conditions had been met	7 (5.3)	14 (10.7)	110 (84.0)	131 (100.0)
Total	181 (2.6)	526 (7.4)	6354 (90.0)	7061 (100.0 %)
Not reported			893	
Non-response rate			7954	
			11.2	

HOSPITAL TYPE

28.4 per cent of the present series of children had been treated at university central hospitals and the Children's Castle of Helsinki (= Type 1) 15.6 per cent in City Hospital of Helsinki 34.5 per cent in hospitals with two or more pediatricians and 21.5 per cent in units with one pediatrician.

Each hospital type was tested against the others.

Admissions for psychic diseases to hospitals of Type 1 were more frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 117.20$ $p < 0.001$).

Admissions for psychic diseases to City Hospital of Helsinki (= Type 2) were less frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 19.77$ $p < 0.001$).

Admissions for psychic diseases to hospitals with two or more pediatricians were less frequent than to the other hospitals. The difference was significant ($\chi^2 = 9.92$ $p < 0.01$).

Admissions for psychic diseases to hospitals with one pediatrician were also less frequent than admissions to the other hospitals. The difference was highly significant ($\chi^2 = 17.37$ $p < 0.001$).

Only one type of hospital was significantly different from the others in the frequency of admissions for functional symptoms: units with one pediatrician had a lower frequency than the other hospitals. The difference was highly significant ($\chi^2 = 15.35$ $p < 0.001$). Table 35.

ADMISSION DELAY

87.2 per cent of the present series of children did not have to wait at all for admission, 4.3 per cent waited for a maximum of one week, 3.4 per cent for 8–30 days and 5.1 per cent for more than a month.

Table 37 gives the percentages of admission delays by diagnostic groups. While only 5.1 per cent of the total series had to wait for admission for more than a month, the corresponding figure among admissions for psychic diseases was 31.8

per cent. While 3.4 per cent of the total series waited for 8–30 days, the figure among admissions for psychic diseases was 15.1 per cent.

When those with no delay in admission were tested against all others, it was found that there were fewer undelayed admissions in the psychic diseases group. The difference was highly significant ($\chi^2 = 382.57$ $p < 0.001$).

A similar difference was seen in admissions for functional diseases: children were admitted less frequently without delay than after a period of queuing up. The difference was highly significant ($\chi^2 = 17.11$ $p < 0.001$).

When the group of children who had had to wait for a maximum of one month was tested against that with a waiting period exceeding one month, it was found that children had had to wait for admission for psychic diseases more frequently for more than a month than for a month. The difference was highly significant ($\chi^2 = 385.94$ $p < 0.001$).

Children with functional symptoms had had to wait for more than a month less frequently than for a maximum of a month. The difference was highly significant ($\chi^2 = 275.39$ $p < 0.001$). Table 36.

POSSIBILITIES OF AN EARLIER DISCHARGE

For purely medical, therapeutic reasons 90.1 per cent of the present series of children could not have been discharged earlier, while 9.9 per cent had some factors prolonging their stay in hospital. The biggest group among these factors was difficult home conditions (4.5 per cent of the total series).

A larger proportion of the children kept in hospital for not purely medical therapy had been admitted for psychic diseases than of the children with no additional indications. The difference was highly significant ($\chi^2 = 13.58$ $p < 0.001$).

The percentages of admissions for functional symptoms did not differ significantly between these two groups. But in the group of children who had to wait for examination, the percentage of functional symptoms (28.2 per cent) was relatively high. Table 38.

TABLE 40

IN THE AREATS SEEK MEDICAL ADVICE IN TIME.

	Mental disorders	Functional symptoms	Other diseases	Total cases
Admissions in time	245 (3.4 %)*	567 (7.7 %)	6505 (88.9 %)	7317 (100.0 %)
Too late	14 (4.9 %)	13 (4.6 %) **	238 (90.5 %)	285 (100.0 %)
Total	259 (3.4 %)	580 (7.6 %)	6763 (89.0 %)	7602 (100.0 %)
			Not reported	352
				7954
			Non-response rate	4.4 %

higher than that of retarded admissions. The difference was highly significant ($\chi^2 = 198.69$ $p < 0.001$) Table 40

HOME NEGLECT

4.2 per cent of the present series of children were judged as neglected at home

Admissions for psychic diseases were more frequent among the neglected than the other children. The difference was highly significant ($\chi^2 = 23.73$ $p < 0.001$)

Admissions for functional symptoms of the children neglected at home were less frequent than those of the other children. The difference was almost significant ($\chi^2 = 1.06$ $p < 0.05$) Table 41

PREVIOUS HOSPITAL ADMISSION OF CHILD FOR THE SAME DISEASE

29.1 per cent of the present series of children had been admitted previously for the same disease, while 70.9 per cent were admitted for the first time for their current disease.

The children who had previously been treated for the same disease were more numerous than those admitted for the first time, among the admissions for psychic diseases. The difference was almost significant ($\chi^2 = 4.39$ $p < 0.05$) Admissions for functional symptoms revealed no significant difference between frequencies of those who had been treated earlier for the same disease and the first admissions, Table 42

TABLE 41

MA ME CH WHEN NEGLECTED HOME?

	Mental disorders	Functional symptoms	Other diseases	Total cases
MA	27 (8.6 %)	14 (4.5 %)	172 (86.9 %)	313 (100.0 %)
ME	237 (3.3 %)	357 (7.7 %)*	6320 (89.0 %)	7214 (100.0 %)
CH	264 (3.5 %)	571 (7.6 %)	6692 (88.9 %)	7527 (100.0 %)
			Not reported	427
				7954
			Non-response rate	5.4 %

READINESS TO SEEK ADMISSION TO HOSPITAL

The purpose of the present investigation was also to find out the extent to which the readiness to seek hospital admission varied from family to family, and the social or socio-psychological background factors associated with such families.

The factors chosen to illustrate this differing tolerance in the parents' attitude to the child's illness and their seeking treatment at home or in hospital for the child were the following:

- was the mother or the father opposed to the child's hospitalization,
- did the parents postpone bringing the child to hospital for economic reasons
- how long did the child suffer from this illness at home before admission to hospital
- had the child been previously hospitalized for the same disease
- had the father, mother or the child's siblings been treated in hospital for disease.

WAS MOTHER OR FATHER OPPOSED TO HOSPITAL ADMISSION OF THE CHILD?

The study revealed that 0.48 per cent of the mothers and 0.75 per cent of the fathers resisted the child's admission to hospital. The attitude of 3.5 per cent of the mothers and 10.6 per cent of the fathers was not known.

DID THE PARENTS DELAY TAKING THE CHILD TO HOSPITAL FOR ECONOMIC REASONS?

Economic reasons had not delayed the child's hospital admission in 90.2 per cent of the cases. The remaining 9.8 per cent of the parents had delayed taking the child to hospital because they feared the expense, or they could not say whether there had been any delay or the delay was for this reason.

Children whose admission had been delayed for economic reasons were admitted for psychic diseases more frequently than those whose admission had not been delayed. The difference was highly significant ($\chi^2 = 22.28$, $p < 0.001$).

In the functional symptoms group there was no difference between those whose admission had been delayed and those whose admission had not been delayed for economic reasons. Table 39.

TIMELINESS OF ADMISSION

In the hospital physicians' opinion 96.3 per cent of the present series of children had been admitted in time and 3.7 per cent too late.

The percentage of retarded admissions was higher than that of timely admissions in the psychic diseases group. The difference was highly significant ($\chi^2 = 65.20$, $p < 0.001$).

In the functional symptoms group the difference was the reverse: the percentage of timely admissions (7.7 per cent) was

TABLE 39
DID PARENTS DELAY TAKING CHILD TO HOSPITAL FOR FEAR OF EXPENSE?

	Mental disorders	Functional symptoms	Other diseases	Total series
N	216 (3.0 %)	332 (7.3 %)	6379 (89.5 %)	7127 (100.0 %)
Y	15 (8.7 %)	15 (8.7 %)	142 (82.6 %)	172 (100.0 %)
Ca not kn	31 (5.6 %)	41 (8.8 %)	529 (87.6 %)	601 (100.0 %)
Total	263 (3.4 %)	388 (7.4 %)	7050 (89.2 %)	7903 (100.0 %)
			Not reported	51
				7954
			Non-response	0.6 %

TABLE 40

DID THEY ARE TO SEE MEDICAL ADVICE TIME?

	Mental disorders	Functional symptoms	Other diseases	Total series
Admission in time	245 (3.4 %)	167 (7.7 %)	6505 (88.9 %)	7317 (100.0 %)
Too late	14 (4.9 %)*	13 (4.6 %)	2.4 (90.5 %)	285 (100.0 %)
Total	259 (3.4 %)	580 (7.6 %)	6763 (89.0 %)	7502 (100.0 %)
			Not reported	352
				7954
			Non-response rate	4.4

higher than that of retarded admissions. The difference was highly significant ($\chi^2 = 198.69$ $p < 0.001$) Table 40

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29.1 per cent of the present series of children had been admitted previously for the same disease, while 10.9 per cent were admitted for the first time for their current disease.

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TABLE 41

HAD THE CHILD BEEN NEGLECTED AT HOME?

	Mental disorders	Functional symptoms	Other diseases	Total series
Yes	27 (8.6 %)	11 (4.5 %)	272 (86.9 %)	313 (100.0 %)
No	237 (3.3 %)	357 (7.7 %)	6420 (89.0 %)	7214 (100.0 %)
Total	264 (3.3 %)	371 (7.6 %)	6692 (88.9 %)	7527 (100.0 %)
			Not reported	427
				7954
			Non-response rate	3.4 %

READINESS TO SEEK ADMISSION TO HOSPITAL

The purpose of the present investigation was also to find out the extent to which the readiness to seek hospital admission varied from family to family and the social or socio-psychological background factors associated with such families.

The factors chosen to illustrate this differing tolerance in the parents' attitude to the child's illness and their seeking treatment at home or in hospital for the child were the following:

- was the mother or the father opposed to the child's hospitalization,
- did the parents postpone bringing the child to hospital for economic reasons
- how long did the child suffer from this illness at home before admission to hospital,
- had the child been previously hospitalized for the same disease
- had the father, mother or the child's siblings been treated in hospital for disease.

WAS MOTHER OR FATHER OPPOSED TO HOSPITAL ADMISSION OF THE CHILD?

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DID THE PARENTS DELAY TAKING THE CHILD TO HOSPITAL FOR ECONOMIC REASONS?

Economic reasons had not delayed the child's hospital admission in 90.2 per cent of the cases. The remaining 9.8 per cent of the parents had delayed taking the child to hospital because they feared the expense or they could not say whether there had been any delay or the delay was for this reason.

Children whose admission had been delayed for economic reasons were admitted for psychic diseases more frequently than those whose admission had not been delayed. The difference was highly significant ($\chi^2 = 22.28$, $p < 0.001$).

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	Mental disorders	Functional symptoms	Other diseases	Total series
No	216 (3.0 %)	532 (7.5 %)	6379 (89.5 %)	7127 (100.0 %)
Yes	15 (8.7 %)	15 (8.7 %)	142 (82.6 %)	172 (100.0 %)
Cannot say	34 (3.6 %)	41 (8.8 %)	529 (87.6 %)	604 (100.0 %)
Total	265 (3.4 %)	588 (7.4 %)	7050 (89.2 %)	7903 (100.0 %)
			Not reported	51
				7954
			Non-response rate	0.6 %

Discussion

a) GENERAL DISCUSSION

Since the purpose was to study factors affecting hospital utilization, morbidity resulting in hospitalization had to be measured.

The present series did constitute a representative sample of what may be termed "morbidity resulting in hospital admission". As the social and psychological factors of the admitted patients and their families were analyzed the factors which affect morbidity resulting in hospital admission were measured simultaneously.

The present series consisted of patients hospitalized for treatment and warrants no conclusions on the general morbidity rate. Many patients stay at home, and many others are treated in outpatient clinics and by private practitioners.

It may be suggested that all cases beyond a certain degree of severity are treated in hospital. However the chances of hospital admission vary in different parts of Finland and it has been shown that distance from hospital plays part in seeking admission (103).

It was found, when the study was based on the hospital physicians' opinion, that factors other than the purely medical formed a relatively small group. The medical indications were responsible for 90.8 per cent of 11 admissions. One of the reasons is perhaps the shortage of beds in children's wards.

It is desirable to admit a child to hospital for indications other than the purely medical. There are two sides to this question: the child's health is naturally of first importance. But cognizant as we are of the heavy expenses the community incurs for hospital therapy, it is

worth pondering whether the children who have, for example, common colds and whose mothers are employed outside the home should not be provided with care and treatment without blocking a very necessary hospital bed with a child patient that could well be nursed at home by a home-help.

If it is seen that the child's mental health is jeopardized unless the child is admitted to hospital for a period — say until another nursing place is provided — the child's interest must be given priority.

b) DISCUSSION OF THE RESULTS

Sex of the child

A study of the percentages previously published in the literature on the sex ratios reveals that boys are usually more numerous, while there are fluctuations depending on the group selected for study. Table 43 quotes some percentages taken from the literature. MacDermott (1963) reported a difference in boy/girl ratios of child patients according to whether or not the parents were skilled workers. It was found that, in the skilled workers group, 74 per cent of the children were boys, while the percentage for the unskilled workers group was 70. In 1967 the same author found while studying psychotic children, that in the two highest social classes the boy/girl ratio showed a higher percentage of boys than in the lower social classes. Lowe (1966) on the other hand, found no statistically significant difference between girls and boys in his material of psychiatric childhood disorders, but when he studied the autistic group separately he found a boy/girl ratio of 2.8/1.0.

TABLE 42
HAD THE CHILD BEEN PREVIOUSLY HOSPITALIZED FOR THIS DISEASE?

	Mental disorders	Functional symptoms	Other diseases	Total series
Yes	88 (40 %)	162 (75 %)	1922 (88.5 %)	2172 (100.0 %)
No	162 (31 %)	390 (74 %)	4744 (89.5 %)	5296 (100.0 %)
Total	250 (3.3 %)	552 (7.4 %)	6666 (89.5 %)	7468 (100.0 %)
			Not reported	486
				7954
			Non-response rate	51 %

PREVIOUS HOSPITAL ADMISSION OF MOTHER

51.5 per cent of the mothers of the present series of children had been treated in hospital (excluding parturitions).

A comparison between the children of the mothers treated in hospital with those who had not been in hospital revealed no significant differences in the frequencies of either psychic diseases or functional symptoms as principal diagnoses.

PREVIOUS HOSPITAL ADMISSION OF FATHER

51.5 per cent of the fathers of the present series of children had been hospitalized at some time during their lives.

The frequencies of mental disorders and functional symptoms as principal diagnosis did not differ significantly

between children of unhospitalized and hospitalized fathers.

PREVIOUS HOSPITAL ADMISSION OF THE CHILD'S SIBLINGS

36.2 per cent of the present series of children had a sibling who had been in hospital. 28.8 per cent either had no siblings or their admissions were not known while 35.0 per cent had siblings but none of them had been hospitalized.

For the statistical test the child patients were divided into those whose sibling had been in hospital and others. The differences between these groups in the frequency of admissions for psychic diseases or functional symptoms were not significant.

Discussion

a) GENERAL DISCUSSION

Since the purpose was to study factors affecting hospital utilization, morbidity resulting in hospitalization had to be measured.

The present series did constitute a representative sample of what may be termed morbidity resulting in hospital admission. As the social and psychological factors of the admitted patients and their families were analyzed, the factors which affect morbidity resulting in hospital admission were measured simultaneously.

The present series consisted of patients hospitalized for treatment and warrants no conclusions on the general morbidity rate. Many patients stay at home, and many others are treated in outpatient clinics and by private practitioners.

It may be suggested that all cases beyond a certain degree of severity are treated in hospital. However the chances of hospital admission vary in different parts of Finland and it has been shown that distance from hospital plays part in seeking admission (103).

It was found, when the study was based on the hospital physicians' opinion, that factors other than the purely medical formed a relatively small group. The medical indications were responsible for 90.8 per cent of all admissions. One of the reasons is perhaps the shortage of beds in children's wards.

Is it desirable to admit a child to hospital for indications other than the purely medical? There are two sides to this question: the child's health is naturally of first importance. But conspicuous as we are of the heavy expenses the community incurs for hospital therapy, it is

worth pondering whether the children who have, for example, common colds and whose mothers are employed outside the home should not be provided with care and treatment without blocking a very necessary hospital bed with a child patient that could well be nursed at home by a home-help.

If it is seen that the child's mental health is jeopardized unless the child is admitted to hospital for a period — say until another nursing place is provided — the child's interest must be given priority.

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Sex of the child

A study of the percentages previously published in the literature on the sex ratios reveals that boys are usually more numerous, while there are fluctuations depending on the group selected for study. Table 43 quotes some percentages taken from the literature. MacDermott (1965) reported a difference in boy/girl ratios of child patients according to whether or not the parents were skilled workers. It was found that, in the skilled workers group, 74 per cent of the children were boys, while the percentage for the unskilled workers group was 70. In 1967 the same author found, while studying psychotic children, that in the two highest social classes the boy/girl ratio showed a higher percentage of boys than in the lower social classes. Lowe (1966) on the other hand, found no statistically significant difference between girls and boys in his material of psychiatric childhood disorders, but when he studied the autistic group separately he found a boy/girl ratio of 2.8/1.0.

TABLE 13

SEX RATIO IN THE CHILD—PSYCHIATRIC SERIES DESCRIBED EARLIER IN THE LITERATURE

Author	Year	Diagnosis group	Boys		Girls	
			Number	%	Number	
Hallgren	1956	Enuresis	100	68.5	46	31.5
Bender	1956	Schizophrenia	95	67.0	47	33.0
Piillips	1957	Autistic children	23	85.0	4	15.0
Ingila et al	1958	Child—psychiatric patients	77	54.0	66	46.0
Eklström et al	1961	Nervous abdominal pain	146	18.7	151	51.3
Hunt	1961	Child guidance clinic patients	398	67.0	193	33.0
Valanne	1961	Child—psychiatric patients	271	56.0	213	44.0

Hunt (1961) from his study of child guidance clinic material, found that boys were heavily over represented. Looking for a reason he came to the conclusion that general behaviour and role expectations *vis-à-vis* sons tend to reduce parental tolerance limits.

In the present series of mental disorders there were also more boys than girls. The ratio was 2/1. The reason for this can be that boys with mental disorders behave in a wilder fashion and therefore cause more stress to the environment than girls. This may be one reason why the physician is approached more readily when a boy is concerned.

It may also be claimed in view of psychiatric diseases that boys are more susceptible to psychic damage. A certain degree of complaining and hypochondria in boys may also be the cause of treatment being sought sooner for them.

It is also possible that boys are generally affected by diseases more often than girls. Some examples from Finland: a study of deaths under the age of one year in 1963 revealed that 837 boys and 659 girls died. For 1964 the figures were 815 boys and 554 girls (94). Bardy (1966) found that 105 boys per 100 girls died at an age under 14 days. Comparing the sex ratios among the mentally subnormal in Finland, Amnell et al. (1965) found that of the 4000 patients examined 3.07 per thousand were men and 2.94 per thousand were women. There were statistically significantly more men than women among the idiots.

Age of the child

In the present study there were significantly more children between 7 and 15 years than children of other age groups in both mental disorders and functional symptoms groups. The reason for this phenomenon may be that mental disorders and many psychosomatic symptoms are more frequent in teenagers (22/66).

Illegitimacy of the child

In the present study there were more social indications for illegitimate than legitimate children. The reason for this may be that the unmarried mothers must be employed outside the home without other facilities than the hospital when the child falls ill. The unmarried mothers may also be uncertain and lacking in spiritual support from their environment. Most single mothers live in poorer economic conditions than married women (10). Päävola (1967) also showed that these unmarried women were often employed in heavy manual work.

The situation of unmarried women is not always so difficult. The community helps them in several ways. They have, for example, priority for day nurseries and kindergartens. Berfenstam and Wilner (1966) showed in their work about Swedish unmarried women that young mothers with one child often got help from their parents and that these unmarried women had managed much better than they had dared to expect at the outset.

Seniority of the child among siblings

The only child was seldom brought to hospital for mental disorders. The reason may be that parents do not see, or refuse to see, the psychic disorder. Other possible reasons may be that the mother has more time to care for the child at home or that she does not let other people see her deficient only child. The only child, furthermore, is often the first child of a young family — so young that the mental disorders have not yet emerged. The parents may also consult an experienced private physician in good time and visit the outpatient department.

The reason why the only child is brought to hospital for functional symptoms more often than the average, is perhaps the very fact that it is the first child of a young couple, and all symptoms are given exceptional attention. Parental uncertainty may be reflected in the fact that they approach a physician more readily and wish their child to be examined at hospital.

When the number of children increases, the tendency to bring a child to hospital for psychic disorders seems to grow slightly. The reason may be that in these families the children approach the age at which mental disorders break out, or that the parents are freer in their attitude to psychic symptoms.

Dvoredsky (1966) presented a review of the literature on the psychic importance of seniority among siblings to the individual. From his review the author came to the conclusion that seniority among siblings is not a separate and unambiguous variable and that it should be considered in relation to other factors.

Importance of the mother

Both Spence and co-workers (88) and Straus and co-workers (92) showed that there was a definite relationship between child's admission to hospital and maternal capacity for home care.

In the present series there were more social indications when the mother was sick or in poor condition than when she was healthy. If the mother was full-time employed there were also more additional

social indications than if she was at home. These results agree with those of Spence and Straus.

The fact that in the present series there were more mental disorders in children who had only a father than in those who had both parents, also indicates the importance of the mother. The result also agrees with Annell's opinion (6) that living without the mother may cause psychic disturbances in children.

One reason for over representation of lonely fathers' children may also be the fact pointed out by Chaskel (12) that the solitary fathers are nowadays more integrated into the framework of social welfare.

Parents' ownership of a private car

In the families with a private car the psychological factors seemed to have some influence on the hospital admission of children. In the families with no private car there were more frequently additional social indications. In order to measure if the ownership of a private car was a sign of wealth in the present series, the car ownership and income of parents were correlated. The phi-coefficient was 0.284. This showed that between these factors there was only a moderate correlation.

From the practical point of view ownership of a car makes it easier to bring the diseased child to a physician's consulting room and to hospital. Both Haavio-Mannila (26) and Laitanen (103) showed that when the distance from home to hospital was long the children were not so readily taken to hospital.

From the beginning of the year 1964 general health insurance was established in Finland and the people were given economic help for journeys to hospital and to physicians. Now it is easier to take a taxi or an ambulance when there is no fear of economic strains because of the journeys.

Ownership of a television set at home

On Finnish Television there is a programme «The TV home doctor» primarily on children's diseases, which was seen

TABLE II

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Parents' ownership of a private car

In the families with a private car the psychological factors seemed to have some influence on the hospital admission of children. In the families with no private car there were more frequently additional social indications. In order to measure, if the ownership of a private car was a sign of wealth in the present series, the car ownership and income of parents were correlated. The phi-coefficient was 0.284. This showed that between these factors there was only a moderate correlation.

From the practical point of view ownership of a car makes it easier to bring the diseased child to a physician's consulting room and to hospital. Both Haavio-Mannila (26) and Väinänen (103) showed that when the distance from home to hospital was long the children were not so readily taken to hospital.

From the beginning of the year 1964 general health insurance was established in Finland and the people were given economic help for journeys to hospital and to physicians. Now it is easier to take a taxi or an ambulance, when there is no fear of economic strains because of the journeys.

Ownership of a television set at home

On Finnish Television there is a programme «The TV home doctor» primarily on children's diseases, which was seen

in 1963 by an average of 451 000 viewers (34). This kind of programme can make parents pay more attention to their children's health and possible symptoms of diseases. Thus the parents bring their child earlier to the physician and to hospital when the disease is not yet so bad.

On the other hand there may be negative effects on the parental mind: creation of futile anxiety by programmes dealing with diseases. Over protective parents can therefore be provoked into unnecessary visits to a doctor. The fact that in the present series there were more admissions for functional symptoms from families with a TV set than from homes with no TV set may partly reflect this mechanism. Also the fact that there were more additional psychological indications in the TV-owners than in others may reflect parental anxiety over protection and fear.

The ownership of a TV set was considered as a socio-psychological factor. In Finland in 1963 the so called intellectual workers were over represented as TV owners (34). Himmelweit et al (1958) studied the differences between TV viewers and non viewers and they came to the conclusion that TV could not abolish the pre-existing differences which were apparently due to social class.

Urban and rural children

Social and psychological indications were more frequent for urban than for rural children. In Helsinki there were more social indications than in other communities. This may reflect the difficulties of home care in cities and also the accumulating social difficulties in big cities. The result from Helsinki agrees with the results from Paris (92).

In the mental disorders group there were no differences between urban and rural children. One might have expected that there would be more psychiatric problems among urban than rural children as pointed out by Miller (66). The fact that the present study deals with hospital patients may obscure the real differences.

Distance from the child's home to nearest physician or hospital

The distance between home and the nearest physician played no part, according to the present material when the child was affected with psychic diseases or functional symptoms. But the distance to hospital was a factor correlated with the child's admission for the above diseases or symptoms. When psychic diseases were in question the child was even taken to a distant hospital. The fact that distance between the hospital and the home of patients with psychic diseases was very great suggests that the hospitals treating these cases should be more evenly distributed. The preponderance of the children brought for treatment over long distances is perhaps explained by the fact that the material includes the psychiatric wards of the Children's Hospital, University of Helsinki, the City Hospital of Helsinki and the Children's Castle in Helsinki which admit patients from all over Finland. During the year studied no child psychiatrists were available in hospitals in Finland except in Helsinki and Turku.

A hospital catering for special patients attracts relatively more of its patients from the immediate area than from more outlying districts. The cases admitted e.g. for psychiatric diseases from North Finland to South Finland hospitals may have been more severe than the cases coming from the more immediate area.

The cerebral palsy children with motor defects, classified under the mental disorders group in the present material form a special category gathered from all over Finland to the Children's Castle in Helsinki. Not until 1966 could special treatment for children with motor defects be had in North Finland. The Pediatric Department of the University of Oulu founded in 1964 started this work in 1966.

South and North Finland

While discussing the difference between South and North Finland the work of Christensen (1956) in Denmark should be remembered. He studied admissions to hospital from two types of districts, a good and a bad in the social sense of the word.

He found that admissions from the poor social areas were twice as frequent as from the better areas. The difference was mainly due to admissions of children under one year of age. Some diseases, such as scarlet fever, tuberculosis and oligophrenia, were equally represented, while others, such as infections of the upper respiratory tract, anaemia and prematurity showed twice this rate of representation. The general finding was that the incidence of infections was three to four times higher in the poor than in the good housing districts.

Haavio-Mannila (1962) found that a remote place of residence did not affect the incidence of diseases, whereas consultation for treatment and location of residence were correlated. The incidence of diseases was highest in all age groups in the northern parts of the country.

The division of the country into North and South Finland was based on differences in the number of hospital beds and physicians per inhabitants. In Lapland the northernmost part of the country there are relatively more hospital beds for children (= Children's Hospital, Rovaniemi) than in the other parts of North Finland. In Lapland, however there are very long distances and the roads are sometimes much more difficult to drive than in South Finland. Väänänen (1963) showed that the distances played significant part in the hospital admissions of children in Lapland. He also showed that, for example, the distance from home to nearest highway had some influence.

In South Finland there were more psychological and particularly social indications than in North Finland. The same indications were more frequent in cities. It may be that behind this result there are special social factors in South Finland and in cities: more crowded dwellings, more employed mothers, and so on.

Hospital type

The higher incidence of psychological factors in university teaching hospitals and in the Children's Castle, Helsinki, may be due to the greater interest the personnel of these hospitals takes in these

factors, but it may even be that patients with additional psychological indications are more easily admitted to this hospital type with special child psychiatric personnel.

A typical city hospital, the City Hospital of Helsinki, is exceptional in that the social indications were more frequent there than elsewhere. Two investigations (Rantasalo 1955, Väänänen 1962) had been carried out at this hospital before and the personnel was well adapted to record the additional social factors in hospital admissions. This may be a contributory factor yet it seems evident that since this hospital gathers its patients from the Helsinki city area with the many difficulties encountered in providing care for the children at home, the social indications were of greater importance for children's admission than in other hospitals. Sociological differences might also affect the result: in Helsinki the help and care of minor illnesses in the family by grandparents, relatives and neighbours are obviously less available than in the less changeable countryside or small-town societies.

The hospitals with one pediatrician form the group of children's hospitals in which additional social factors played a great part for the child's admission. The reason for this may be that the rural district surrounding these hospitals is mostly both medically and socially underdeveloped.

Most mental disorders were treated in university hospitals and in the Children's Castle, Helsinki. Hospitals with several pediatricians came next and only very few patients with mental disorders were treated in the City Hospital of Helsinki and in hospitals with one pediatrician. Especially in the units with one pediatrician there may even be great difficulties in treating patients with mental disorders since there are so many acute diseases and so few specially trained personnel.

There can also be some pressure on pediatric wards (by mentally subnormal children) because of the lack of beds in the institutions for the mentally handicapped. In his study of the mentally subnormal in Finland in 1966 Tarvainen (1966) came to the conclusion that 10,200

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beds for these patients were required in Finland. The number of beds in institutions was in June 1964 about 2300.

Thus some children who must be cared for at home due to lack of beds in the institutions may sometimes be admitted to pediatric wards — not for purely medical reasons but because of some kind of family exhaustion.

Length of hospital stay

As far as is known, the length of hospital stay and social conditions of mentally disturbed children have not been studied previously. The studies of adult psychiatric patients were reviewed by Vornbrock and Wences (1967). In their own study the authors found that the age of patients rather than education or occupational status was the significant factor in relation to length of hospital stay.

In the present study delays in discharge from hospital were frequent in both mental disorders and functional symptoms. In both diagnostic groups the most important reason was the waiting for examinations. In mental disorders this group was 6.8 % and in functional symptoms 28.2 %. Certain home conditions and distance from hospital to home also contributed to the overlong stay in hospital. Finland may therefore need more examination facilities and disintegration of hospitals for mental disorders in children.

Parental readiness to seek admission for their child

The parental attitude to hospital admission of their child was generally favourable. Only less than one per cent of parents opposed the admission. If the mental disorders and functional symptoms groups are taken together only 13 fathers and 7 mothers were in opposition to the admission.

Two factors which probably influenced this result were the shortage of hospital beds and the fact that hospital treatment is relatively inexpensive in Finland. The patient or the parents of the patient pay only 10–20 per cent of all hospital charges and the community pays the rest. A hospital day costs in Finland 6 Fmk (equivalent to 1.86 U.S. \$).

Straus et al. (92) emphasized that there are factors in certain families which can lead to high incidence of hospital admission of family members. In these cases the purely medical indications for admission are too slight. The same child can also be admitted several times for the same disease and on too slight medical basis.

In the present study there was a high incidence of delays for economic reasons of admissions too late, of home neglect of the child and of previous admissions of the child in the mental disorders group. This all shows that this diagnostic group has numerous special problems.

The incidence of hospital admissions of other family members was low which may mean that the readiness to seek hospital admission was in the present study more connected with the child and its disease than with some general factor in the family.

Summary

A study of the social and psychological factors in hospital admission of children was made in Finland 1963-64. During four months (April, May and August 1963 and January 1964) a comprehensive questionnaire with 70 questions was completed for all children admitted to 21 children's hospitals. Only 2 children's hospitals in the whole country could not participate in the study. The questions investigated the socio-economic and socio-psychological factors in the family, the child's diseases and parental attitudes towards child, hospital and disease. The study comprised altogether 7954 children.

In the present study the collected data were analysed by computer to find those additional social and psychological factors which affect hospital admission of children. Two diagnosis groups were also analysed more closely for social and socio-psychological background factors: mental disorders and so called functional symptoms in the childhood.

1. SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION

In the total series of patients there were more boys than in the total Finnish population when both sexes were divided in different age groups.

Social indications in the hospital admission were more frequent for illegitimate than legitimate children, and also more frequent when the only child was involved than when the child was one of several siblings. Additional social factors contributed to hospital admission more often when the mother was sick or in poor condition than if she was healthy.

Psychological factors in the family were more frequent in the higher income

bracket than in the lower one. Social factors were more frequent in the lower income bracket than in the higher one. Social factors influenced hospital admission of farmers' children less frequently than non-farmers.

If the family had a private car there were more frequently additional psychological factors than in those families which had no private car. There were more social factors in those families which did not have a car than in those which did.

Ownership of a TV set was considered as a socio-psychological factor. When the family had a TV set there were more frequently additional psychological factors than when the family had no TV set.

Social and psychological factors were more frequent for urban than for rural children. When Helsinki, a small metropolis, was tested against all other community types, it was found that there were more social indications for Helsinki children than for children from other communities.

To study the influence of public health resources the country was divided into two parts. The part with fewer physicians and fewer hospital beds was named North Finland and the second part South Finland. Both social and psychological indications were more frequent in South Finland than in North Finland.

The 21 participating hospitals were divided into four groups according to their working facilities. Psychological indications were more frequent in the university hospital and in a special pediatric hospital in Helsinki, named Childrens' Castle, than in other hospital types. Social indications were more frequent in the City Hospital of Helsinki and in the hospitals with only one pediatrician than in other hospital types.

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II SOCIO-ECONOMIC AND SOCIO-PSYCHOLOGICAL FACTORS IN MENTAL DISORDERS AND FUNCTIONAL SYMPTOMS

In both groups there were more frequently additional social and psychological factors in the hospital admission than admissions for purely medical indications.

In the diagnosis group of mental disorders there were more boys than girls, more children of 7—15 years of age than younger and more eldest children than others. There were also more children of unmarried than married fathers and more children of fathers possessing a university degree than with lower educational level.

In this diagnosis group there were more children from upper than from lower income families, more children from such families which had a TV set than from families with no TV. The same difference as in the ownership of a TV set was true of the ownership of a summer cottage. The children had more frequently a distance from home to hospital exceeding 100 km than maximum 100 km.

In mental disorders group children had to wait for admission more often and for a longer time than in other diseases. There were often factors which delayed the discharge of the child from hospital. Parents had often delayed hospital admission for economic reasons. The child was taken to hospital more often too late than in time and the home care of the child was frequently neglected. The children

had already been in hospital more frequently than admitted for the first time for this disease.

In the diagnosis group of functional symptoms there were less children under one year than one year and older. There were more children between 7—15 years of age than under 7 years. The only child was admitted less frequently for functional symptoms than other children. The group contained more children from families with one inhabitant per room than children from families with more than one inhabitant per room. Children with a TV set at home were admitted more frequently than those who had no TV set at home. The ownership of a summer cottage had the same influence.

The group contained a larger number of children living at a distance of more than 100 km from hospital than children with a maximum distance of 100 km between home and hospital, more children from Helsinki than from other communities and more children from North Finland than from South Finland.

In hospitals with one pediatrician there were less children with functional symptoms than in other hospital types.

The children had to wait less frequently for more than one month than for a maximum of one month and admissions in time were more frequent than retarded admissions. Admissions of children whose care was neglected at home were less frequent than admissions of other children.

Acknowledgements

The subject for this study was suggested by my chief, Professor Ole Wasz Höckert, M.D. Head of the Department of Pediatrics University of Oulu. During the course of the work he has advised and encouraged me, for which I am extremely grateful.

Professor Niilo Hallman M.D., Head of the Children's Hospital, University of Helsinki has given me practical guidance and constructive and valuable criticism of the study at all stages. My respectful thanks are due to him for his help.

The biostatistics involved, ever since the collection of data was planned, were handled by Timo Partanen, M.Sc., of the Institute of Occupational Health, Helsinki. He spared no effort to help me in the various statistical problems. Mathematical expertise has also been offered to me by Pertti Hyyrynen, M.Sc., of the Department of Mathematics, and the Computer Centre of the University of Oulu, and I owe a debt of gratitude to them both.

Since my study also concerned aspects of child-psychiatry I sought advice from Eero Valanne, M.D., Child Psychiatrist of the Children's Hospital, University of Helsinki. I am greatly indebted to him for encouragement and support.

Associated Professor Kauko Kouvalainen M.D., of the Pediatric Clinics, University of Turku has helped me with critical advice in his capacity of faculty expert, for which I am very grateful.

Acting Professor Kai Sievers, M.D. Department of Hygiene and Social Medicine, University of Oulu has gone over certain passages of the book with me and suggested useful corrections. I thank him for his interest and help.

The manuscript was translated into English by Hilkka Kontiopää, M.A. (Helsinki) and John Suter Hon.B.A.Econ. (Dub.) My warmest thanks are due to them, to the personnel of the Medical Library University of Oulu who have helped me obtain the necessary literature and to the secretaries who have retyped the manuscript.

The study would not have been possible had not numerous physicians and nurses, unknown to me, carefully completed the relevant forms and questionnaires. This involved a great many extra working hours for already overworked staff. My special gratitude is due to the chief physicians of the 21 pediatric hospitals concerned, whose support was required to make the study possible.

Financial support was received from the Ane and Signe Gyllenberg Foundation, Foundation for Pediatric Research in Finland, Medical Suppliers Orion Ltd., and Medical Research Foundation of Oulu. I am greatly indebted to them all.

Oulu, January 1969

GEORG ROSENBERG

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INVESTIGATION OF INDICATIONS FOR HOSPITAL ADMISSION OF CHILDREN

JOURNAL NO.

HOSPITAL AND WARD

DATE OF ADMISSION

SEX
(CIRCLE)

☐ GIRL

☐ BOY

IS THE CHILD

☐ UNMARRIED

☐ REMARRIED

CHILD'S AGE ON ADMISSION

☐ UNDER 15 DAYS

☐ 36 MONTHS

☐ 5 YEARS

☐ ONE MONTH

☐ 3 YEARS

☐ 9 YEARS

☐ 2 MONTHS

☐ 42 MONTHS

☐ 10 YEARS

☐ 3 MONTHS

☐ 4 YEARS

☐ 11 YEARS

☐ 4-5 MONTHS

☐ 54 MONTHS

☐ 12 YEARS

☐ 6-11 MONTHS

☐ 6 YEARS

☐ 13 YEARS

☐ 12-17 MONTHS

☐ 6 YEARS

☐ 14 YEARS

☐ 18-24 MONTHS

☐ 7 YEARS

☐ 15 YEARS

CHILD'S DOCTOR

PARENT/FOSTER PARENT/PRESENT OCCUPATION

FATHER

MOTHER

PARENT/FOSTER PARENT/ OCCUPATION
BY INDUSTRY

FATHER MOTHER

- | | | |
|--------------------------|--------------------------|--|
| <input type="checkbox"/> | <input type="checkbox"/> | AGRICULTURE AND FORESTRY
FISHING |
| <input type="checkbox"/> | <input type="checkbox"/> | MANUFACTURING INDUSTRY |
| <input type="checkbox"/> | <input type="checkbox"/> | UTIL. ELECTRICITY GAS AND
WATER SERVICES HANDICRAFT |
| <input type="checkbox"/> | <input type="checkbox"/> | BUILDING |
| <input type="checkbox"/> | <input type="checkbox"/> | COMMERCE |
| <input type="checkbox"/> | <input type="checkbox"/> | COMMUNICATIONS |
| <input type="checkbox"/> | <input type="checkbox"/> | SERVICES (SOCIAL, INDUSTRIAL,
PRIVATE) |
| <input type="checkbox"/> | <input type="checkbox"/> | NO OCCUPATION |
| <input type="checkbox"/> | <input type="checkbox"/> | NOT KNOWN |

16. PARENT/FOSTER PARENT/ OCCUPATION-
ALL POSITION

FATHER MOTHER

- | | | |
|--------------------------|--------------------------|-------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | EMPLOYED, SELF-EMPLOYED |
| <input type="checkbox"/> | <input type="checkbox"/> | MANAGER, EXECUTIVE |
| <input type="checkbox"/> | <input type="checkbox"/> | WORKER |
| <input type="checkbox"/> | <input type="checkbox"/> | ASSISTING FAMILY MEMBER |
| <input type="checkbox"/> | <input type="checkbox"/> | NO OCCUPATION |
| <input type="checkbox"/> | <input type="checkbox"/> | NOT KNOWN |

CODES

1

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INVESTIGATION OF INDICATIONS FOR HOSPITAL ADMISSION OF CHILDREN

JOURNAL NO.

HOSPITAL AND WARD

DATE OF ADMISSION

SEX
(CIRCLE)

☐ GIRL

☐ BOY

IS THE CHILD

☐ LEGITIMATE

☐ ILLEGITIMATE

CHILD'S AGE ON ADMISSION

☐ UNDER 3 DAYS

☐ 30 MONTHS

☐ 8 YEARS

☐ ONE MONTH

☐ 3 YEARS

☐ 9 YEARS

☐ 2 MONTHS

☐ 42 MONTHS

☐ 10 YEARS

☐ 3 MONTHS

☐ 4 YEARS

☐ 11 YEARS

☐ 4-5 MONTHS

☐ 54 MONTHS

☐ 12 YEARS

☐ 6-11 MONTHS

☐ 5 YEARS

☐ 13 YEARS

☐ 12-17 MONTHS

☐ 6 YEARS

☐ 14 YEARS

☐ 18-24 MONTHS

☐ 7 YEARS

☐ 15 YEARS

CHILD'S DOMICILE

PARENTS/FOSTER PARENTS' PRESENT OCCUPATION

FATHER

MOTHER

PARENTS/FOSTER PARENTS' OCCUPATION
BY INDUSTRY

ATHER MOTHER

- ☐ ☐ AGRICULTURE AND FORESTRY
FISHING
- ☐ ☐ MANUFACTURING INDUSTRY
(EXCL. ELECTRICITY, GAS AND
WATER SERVICES), HANDICRAFT
BUILDING
- ☐ ☐ COMMERCE
- ☐ ☐ COMMUNICATIONS
- ☐ ☐ SERVICES (SOCIAL, INDUSTRIAL,
PRIVATE)
- ☐ ☐ NO OCCUPATION
- ☐ ☐ NOT KNOWN

PARENTS/FOSTER PARENTS' OCCUPATION-
AL POSITION

ATHER MOTHER

- ☐ ☐ EMPLOYED, SELF-EMPLOYED
- ☐ ☐ MANAGER, EXECUTIVE
- ☐ ☐ WORKER
- ☐ ☐ ASSISTING FAMILY MEMBER
- ☐ ☐ NO OCCUPATION
- ☐ ☐ NOT KNOWN

CODES

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11. MARITAL STATUS OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER MOTHER <input type="checkbox"/> <input type="checkbox"/> MARRIED <input type="checkbox"/> <input type="checkbox"/> SINGLE <input type="checkbox"/> <input type="checkbox"/> WIDOWER/WIDOW <input type="checkbox"/> <input type="checkbox"/> JUDICIAL SEPARATION <input type="checkbox"/> <input type="checkbox"/> DIVORCED <input type="checkbox"/> <input type="checkbox"/> DEAD <input type="checkbox"/> <input type="checkbox"/> NOT KNOWN		12. DO THE CHILD'S PARENTS LIVE IN THE CHILD'S HOME? <input type="checkbox"/> BOTH DO <input type="checkbox"/> MOTHER ONLY <input type="checkbox"/> FATHER ONLY <input type="checkbox"/> CHILD LIVES WITH RELATIVES OR FOSTER PARENTS <input type="checkbox"/> CHILD LIVES IN INSTITUTIONAL CARE (E.G. CHILDREN'S HOME)		24	25	26
13. AGE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER — YEARS MOTHER YEARS				27	28	
				29	30	
14. SCHOOL ATTENDANCE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER MOTHER <input type="checkbox"/> <input type="checkbox"/> AMBULATORY SCHOOL ONLY <input type="checkbox"/> <input type="checkbox"/> PRIMARY SCHOOL, LOWER FORMS <input type="checkbox"/> <input type="checkbox"/> COMPLETE <input type="checkbox"/> <input type="checkbox"/> SECONDARY SCHOOL, LOWER FORMS <input type="checkbox"/> <input type="checkbox"/> FIVE FORMS (MIDDLE SCHOOL) <input type="checkbox"/> <input type="checkbox"/> MORE THAN FIVE FORMS BUT NO MATRICULATION <input type="checkbox"/> <input type="checkbox"/> MATRICULATION, BUT NO UNIV. OR OTHER DEGREE <input type="checkbox"/> <input type="checkbox"/> UNIVERSITY OR OTHER DEGREE <input type="checkbox"/> <input type="checkbox"/> NOT KNOWN OTHER SCHOOLS FATHER MOTHER				31	32	
				33		
				34		
15. DISTANCE FROM HOSPITAL TO CHILD'S HOME/ NURSING HOME <input type="checkbox"/> UNDER 1/2 KM <input type="checkbox"/> 16-30 KM <input type="checkbox"/> 1/2-1 KM <input type="checkbox"/> 31-100 KM <input type="checkbox"/> 3-3 KM <input type="checkbox"/> 101-300 KM <input type="checkbox"/> 4-10 KM <input type="checkbox"/> 201 KM OR MORE <input type="checkbox"/> 11-15 KM <input type="checkbox"/> NOT KNOWN		16. DISTANCE FROM CHILD'S HOME/NURSING HOME TO THE NEAREST a. NEIGHBOUR KM b. TELEPHONE (UNLESS AT HOME) KM MAJOR VILLAGE OR POPULATION CENTRE KM c. PHYSICIAN KM		35		
					36	
					37	
					38	
					39	
17. MEANS OF TRANSPORT ONE OR SEVERAL, BY WHICH THE CHILD WAS BROUGHT TO HOSPITAL (CARRIED, BY PARENTS' CAR, TAXI, HORSE CART OR SLEIGH, CHAIR SLID ETC.) OVER WHAT DISTANCE. KM				40	41	
				42	43	

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

11. NUMBER OF YEARS THE FAMILY HAS LIVED IN ITS PRESENT DOMICILE _____ YEARS		44	45																																	
12. ORIGINITY OF THE CHILD AMONG SIBLINGS IF ANY <input type="checkbox"/> NO SIBLINGS		46	47																																	
13. NUMBER OF CHILDREN UNDER 15 YEARS LIVING WITH THE CHILD'S FAMILY _____ CHILDREN	14. FACILITIES IN THE CHILD'S HOME <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;"></th> <th style="width: 10%; text-align: center;">YES</th> <th style="width: 10%; text-align: center;">NO</th> </tr> </thead> <tbody> <tr> <td>a. ELECTRICITY</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td>b. TELEPHONE</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td> RUNNING WATER</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td>c. TELEVISION</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td colspan="3" style="text-align: center; padding-top: 5px;">DOES THE FAMILY OWN</td> </tr> <tr> <td>a. PRIVATE CAR</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td>c. SUMMER COTTAGE</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </tbody> </table>			YES	NO	a. ELECTRICITY	<input type="checkbox"/>	<input type="checkbox"/>	b. TELEPHONE	<input type="checkbox"/>	<input type="checkbox"/>	RUNNING WATER	<input type="checkbox"/>	<input type="checkbox"/>	c. TELEVISION	<input type="checkbox"/>	<input type="checkbox"/>	DOES THE FAMILY OWN			a. PRIVATE CAR	<input type="checkbox"/>	<input type="checkbox"/>	c. SUMMER COTTAGE	<input type="checkbox"/>	<input type="checkbox"/>	48	49	50	51	52	53	54	55	56	57
	YES	NO																																		
a. ELECTRICITY	<input type="checkbox"/>	<input type="checkbox"/>																																		
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a. PRIVATE CAR	<input type="checkbox"/>	<input type="checkbox"/>																																		
c. SUMMER COTTAGE	<input type="checkbox"/>	<input type="checkbox"/>																																		
15. NUMBER OF FAMILY MEMBERS (ALL CHILDREN INCLUDED) _____ PERSONS		16. NUMBER OF ROOMS AT THE FAMILY'S DISPOSAL, INCLUDING KITCHEN (BUT EXCLUDING KITCHENETTE, AREA FOR BED, BATHROOM, L.A. TOILET AND ROOMS RENTED OUT) _____ ROOMS		58	59																															
17. PARENTS' MONTHLY EARNINGS, TOTAL _____ CLOPSEW HS		18. FOR CHILD LIVING IN FARMER FAMILY NUMBER OF HECTARES OF a. THE FARM'S TOTAL AREA _____ HA b. AREA UNDER PLOUGH _____ HA		60	61	62	63	64	65	66	67	68	69	70	71																					
19. IF MOTHER GAINFULL EMPLOYED OUTSIDE HOME <input type="checkbox"/> NO <input type="checkbox"/> PRIMARILY PART-TIME <input type="checkbox"/> FULL-TIME		20. IF MOTHER IS EMPLOYED OUTSIDE HOME, IS THE CHILD DURING MOTHER'S WORKING HOURS <input type="checkbox"/> AT HOME TENDED BY SOMEONE ELSE <input type="checkbox"/> AT HOME ALONE OR WITH OTHER CHILDREN <input type="checkbox"/> IN DAY NURSERY OR THE LIKE <input type="checkbox"/> IN RELATED OR OTHER FAMILY		COLUMN 6		72	73	74	75	76	77	78	79	80																						
(Additional space for item 19)		(Additional space for item 20)		81	82	83	84	85	86	87	88	89	90																							

11. MARITAL STATUS OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER MOTHER <input type="checkbox"/> <input type="checkbox"/> MARRIED <input type="checkbox"/> <input type="checkbox"/> SINGLE <input type="checkbox"/> <input type="checkbox"/> WIDOWER/WIDOW <input type="checkbox"/> <input type="checkbox"/> JUDICIAL SEPARATION <input type="checkbox"/> <input type="checkbox"/> DIVORCED <input type="checkbox"/> <input type="checkbox"/> DEAD <input type="checkbox"/> <input type="checkbox"/> NOT KNOWN		12. DO THE CHILD'S PARENTS LIVE IN THE CHILD'S HOME? <input type="checkbox"/> BOTH DO <input type="checkbox"/> MOTHER ONLY <input type="checkbox"/> FATHER ONLY <input type="checkbox"/> CHILD LIVES WITH RELATIVES OR FOSTER PARENTS <input type="checkbox"/> CHILD LIVES IN INSTITUTIONAL CARE (E.G. CHILDREN'S HOME)		2	23	24
13. AGE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER YEARS MOTHER YEARS				27	28	
				29	30	
14. SCHOOL ATTENDANCE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE) FATHER MOTHER <input type="checkbox"/> <input type="checkbox"/> AMBULATORY SCHOOL ONLY <input type="checkbox"/> <input type="checkbox"/> PRIMARY SCHOOL, LOWER FORMS <input type="checkbox"/> <input type="checkbox"/> COMPLETE <input type="checkbox"/> <input type="checkbox"/> SECONDARY SCHOOL, LOWER FORMS <input type="checkbox"/> <input type="checkbox"/> FIVE FORMS (MIDDLE SCHOOL) <input type="checkbox"/> <input type="checkbox"/> MORE THAN FIVE FORMS BUT NO MATRICULATION <input type="checkbox"/> <input type="checkbox"/> MATRICULATION, BUT NO UNIV. OR OTHER DEGREE <input type="checkbox"/> <input type="checkbox"/> UNIVERSITY OR OTHER DEGREE <input type="checkbox"/> <input type="checkbox"/> NOT KNOWN OTHER SCHOOLS FATHER MOTHER				31	32	
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15. DISTANCE FROM HOSPITAL TO CHILD'S HOME/ NURSING HOME <input type="checkbox"/> UNDER 1/2 KM <input type="checkbox"/> 16-30 KM <input type="checkbox"/> 1/2-1 KM <input type="checkbox"/> 31-100 KM <input type="checkbox"/> 2-3 KM <input type="checkbox"/> 101-300 KM <input type="checkbox"/> 4-10 KM <input type="checkbox"/> 301 KM OR MORE <input type="checkbox"/> 11-15 KM <input type="checkbox"/> NOT KNOWN		16. DISTANCE FROM CHILD'S HOME/NURSING HOME TO THE NEAREST NEIGHBOUR KM b. TELEPHONE (UNLESS AT HOME) KM MAJOR VILLAGE OR POPULATION CENTRE KM d. PHYSICIAN KM		35		
					36	
					37	
					38	
					39	
17. MEANS OF TRANSPORT ONE OR SEVERAL, BY WHICH THE CHILD WAS BROUGHT TO HOSPITAL (CARRIED BY PARENTS' CAR, TAXI, HORSE CART OR SLEIGH, CHAIR SLED ETC.) OVER WHAT DISTANCE, KM				40	41	
				42	43	

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

31. WERE THE PARENTS OPPOSED TO THE CHILD'S HOSPITALIZATION?

MOTHER FATHER

☐ ☐ NO

☐ ☐ YES, FOR THIS REASON _____

☐ ☐ CANNOT SAY

22 23

32. HAVE THE CHILD'S PARENTS BEEN TREATED IN HOSPITAL FOR ILLNESS (EXCLUDING CHILDRENTING)?

MOTHER FATHER

☐ ☐ YES

☐ ☐ NO

☐ ☐ NOT KNOWN

24

33. HAS ANY OF THE CHILD'S SIBLINGS BEEN TREATED IN HOSPITAL FOR ILLNESS?

☐ YES

☐ NO ONE

☐ THERE ARE NO SIBLINGS

☐ NOT KNOWN

25

34. WHO WAS/WERE INTERVIEWED?

35. ADDITIONAL INFORMATION

DATE _____ 196__

INTERVIEWER'S NAME AND POSITION _____

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

7a. IF MOTHER IS EMPLOYED OUTSIDE HOME, HOW LONG HAS SHE BEEN SO EMPLOYED

--- -- -- DAYS/WEEKS/MONTHS/YEARS

7b. HOW LONG DID THE CHILD SUFFER FROM THIS ILLNESS AT HOME, BEFORE ADMISSION TO HOSPITAL

--- -- -- DAYS/WEEKS/MONTHS/YEARS

8. HAS THE CHILD BEEN PREVIOUSLY TREATED IN HOSPITAL FOR THIS ILLNESS

☐ YES

☐ NO

9. HAD SOMEONE ADVISED THE PARENTS TO TAKE THE CHILD TO HOSPITAL

☐ NO ONE

☐ PHYSICIAN

☐ NURSE, PUBLIC HEALTH NURSE, DEACONESS, HOUSEKEEPER ETC.

☐ HEALER

☐ MOTHER-IN-LAW THE CHILD'S MATERNAL OR PATERNAL GRANDMOTHER

☐ SOMEONE ELSE

☐ NOT KNOWN

10. WHO WAS FIRST CONSULTED FOR MEDICAL HELP AFTER THE CHILD HAD FALLEN ILL

☐ 1 PHYSICIAN

☐ 2 PUBLIC HEALTH NURSE/PHO-WIFE/DEACONESS

☐ 3 HEALER

☐ 4 PHARMACY

☐ 5-9 SOMEONE ELSE

HOW LONG HAD THE ILLNESS LASTED BY THEN

--- -- -- DAYS/WEEKS/MONTHS/YEARS

11. WAS PHYSICIAN CONSULTED FOR THE CHILD'S ILLNESS

☐ YES

☐ NO

12a. DID PARENTS POSTPONE TAKING THE CHILD TO HOSPITAL FOR FEAR OF EXPENSES

☐ YES

☐ NO

☐ CANNOT SAY

b. FOR SOME OTHER REASON

13. ARE THE CHILD'S PARENTS AND SIBLINGS AT THE MOMENT HEALTHY SICKLY OR ILL?

SIBLINGS

	FATHER	MOTHER	ELDEST	2	3	4	5	6	7	8
HEALTHY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SICKLY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ILL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SIBLINGS

	10	11	12	13
HEALTHY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SICKLY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ILL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14. Healthy here refers to person who does not consider himself ill and manages his everyday work satisfactorily. Person whose described state of health does not enable him to manage his everyday work satisfactorily is regarded as sickly. Person who does not consider himself ill and manages his everyday work satisfactorily is regarded as healthy.

TO BE COMPLETED BY PHYSICIAN ON THE CHILD'S DISCHARGE

(or at the latest, on the day the form is due to be returned)

1. DIAGNOSIS AT OUTPATIENT CLINIC ON ADMISSION	25	26
DIAGNOSIS ON DISCHARGE (IF DISCHARGED)	27	28
DO YOU FIND THAT THE CHILD WAS ADMITTED (CHECK)	29	
<input type="checkbox"/> ON PURELY MEDICAL INDICATIONS		
<input type="checkbox"/> PARTLY ALSO FOR SOCIAL REASONS		
<input type="checkbox"/> DECEIVELY FOR SOCIAL REASONS		
<input type="checkbox"/> PARTLY OR DECEIVELY DUE TO PSYCHOLOGICAL FACTORS IN THE FAMILY		
DO YOU FIND THAT THE PARENTS	46	
<input type="checkbox"/> CONSULTED THE PHYSICIAN / THE HOSPITAL IN TIME		
<input type="checkbox"/> CONSULTED THE PHYSICIAN / THE HOSPITAL TOO LATE		
DO YOU FIND THAT THE CHILD HAD APPARENTLY BEEN NEGLECTED AT HOME	47	
<input type="checkbox"/> YES		
<input type="checkbox"/> NO		
COULD THE CHILD HAVE BEEN DISCHARGED EARLIER (TO BE COMPLETED ONLY IF THE CHILD HAS BEEN DISCHARGED)	48	
<input type="checkbox"/> YES, IF THE CHILD'S HOME CONDITIONS HAD BEEN BETTER		
<input type="checkbox"/> YES, IF THE CHILD'S HOME HAD BEEN BETTER LOCATED		
<input type="checkbox"/> YES, HAD THE CHILD NOT ACQUIRED AN INFECTION IN HOSPITAL		
<input type="checkbox"/> YES, IF THERE HAD BEEN NO WAITING PERIOD BEFORE EXAMINATIONS		
<input type="checkbox"/> YES, IF THE FOLLOWING CONDITIONS HAD BEEN MET _____		
<input type="checkbox"/> NO		

DATE ____/____/____

PHYSICIAN'S SIGNATURE _____

TO BE COMPLETED BY WARD SISTER ON THE CHILD'S DISCHARGE

(or at the latest, on the day the form is due to be returned)

<p>40. ■ THE CHILD HAS BEEN DISCHARGED. HOW LONG DID HE STAY</p> <p>— — — — DAYS</p> <p>IF HE HAS NOT BEEN DISCHARGED, HE REMAINED IN THE HOSPITAL ON (DATE) — — — / — — — 196 —</p>	27	28	29																					
<p>41. HOW LONG DID THE CHILD HAVE TO WAIT FOR ADMISSION</p> <p>— — — — DAYS/WEEKS/MONTHS</p>	30																							
<p>42. WAS THE PARENTS/FOSTER PARENTS' ATTITUDE TO HOSPITAL AND HOSPITAL PERSONNEL</p> <p><input type="checkbox"/> 1 FAVOURABLE</p> <p><input type="checkbox"/> 2 INDIFFERENT</p> <p><input type="checkbox"/> 3 NEGATIVE</p> <p><input type="checkbox"/> 4 IMPOSSIBLE TO SAY</p> <p><input type="checkbox"/> 5 THE CHILD CAME FROM AN INSTITUTION</p>	31																							
<p>43. WAS THE PARENTS/FOSTER PARENTS' ATTITUDE TO THE CHILD</p> <table border="0"> <thead> <tr> <th>FATHER</th> <th>MOTHER</th> <th></th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> 1</td> <td><input type="checkbox"/> 1</td> <td>UNUSUALLY PROTECTIVE</td> </tr> <tr> <td><input type="checkbox"/> 2</td> <td><input type="checkbox"/> 2</td> <td>UNUSUALLY SPOILING</td> </tr> <tr> <td><input type="checkbox"/> 3</td> <td><input type="checkbox"/> 3</td> <td>NORMAL</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>SLIGHTING OR INDIFFERENT</td> </tr> <tr> <td><input type="checkbox"/> 4</td> <td><input type="checkbox"/> 4</td> <td>IMPOSSIBLE TO SAY</td> </tr> <tr> <td><input type="checkbox"/> 5</td> <td></td> <td>THE CHILD CAME FROM AN INSTITUTION</td> </tr> </tbody> </table>	FATHER	MOTHER		<input type="checkbox"/> 1	<input type="checkbox"/> 1	UNUSUALLY PROTECTIVE	<input type="checkbox"/> 2	<input type="checkbox"/> 2	UNUSUALLY SPOILING	<input type="checkbox"/> 3	<input type="checkbox"/> 3	NORMAL	<input type="checkbox"/>	<input type="checkbox"/>	SLIGHTING OR INDIFFERENT	<input type="checkbox"/> 4	<input type="checkbox"/> 4	IMPOSSIBLE TO SAY	<input type="checkbox"/> 5		THE CHILD CAME FROM AN INSTITUTION	32	33	
FATHER	MOTHER																							
<input type="checkbox"/> 1	<input type="checkbox"/> 1	UNUSUALLY PROTECTIVE																						
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<input type="checkbox"/> 3	<input type="checkbox"/> 3	NORMAL																						
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<input type="checkbox"/> 4	<input type="checkbox"/> 4	IMPOSSIBLE TO SAY																						
<input type="checkbox"/> 5		THE CHILD CAME FROM AN INSTITUTION																						
<p>44. ON DISCHARGE THE CHILD WAS</p> <p><input type="checkbox"/> 1 CONVALESCENT</p> <p><input type="checkbox"/> 2 UNIMPROVED</p> <p><input type="checkbox"/> 3 UNTREATED</p> <p><input type="checkbox"/> 4 DEAD</p> <p><input type="checkbox"/> 5 REMAINED IN HOSPITAL AFTER THE FORM WAS RETURNED</p> <p>DATE — — / — — 196 —</p> <p>— — — — — WARD SISTER'S SIGNATURE</p>	34																							

TO BE COMPLETED BY PHYSICIAN ON THE CHILD'S DISCHARGE

(or at the latest, on the day the form is due to be returned)

DIAGNOSIS T OUTPATIENT CLINIC ON ADMISSION	23	24
DIAGNOSIS ON DISCHARGE (IF DISCHARGED)	27	28
DO YOU FIND THAT THE CHILD WAS ADMITTED (CROSS) <input type="checkbox"/> ON PURELY MEDICAL INDICATIONS <input type="checkbox"/> PARTLY ALSO FOR SOCIAL REASONS <input type="checkbox"/> DISCREPANT FOR SOCIAL REASONS <input type="checkbox"/> PARTLY OR DISCREPANT DUE TO PSYCHOLOGICAL FACTORS IN THE FAMILY	29	
DO YOU FIND THAT THE PARENTS <input type="checkbox"/> CONSULTED THE PHYSICIAN / THE HOSPITAL IN TIME <input type="checkbox"/> CONSULTED THE PHYSICIAN / THE HOSPITAL TOO LATE	30	
DO YOU FIND THAT THE CHILD HAD APPARENTLY BEEN NEGLECTED - NONE <input type="checkbox"/> YES <input type="checkbox"/> NO	31	
COULD THE CHILD HAVE BEEN DISCHARGED EARLIER? (TO BE COMPLETED ONLY IF THE CHILD HAS BEEN DISCHARGED) <input type="checkbox"/> YES, IF THE CHILD'S HOME CONDITIONS HAD BEEN BETTER <input type="checkbox"/> YES, IF THE CHILD'S HOME HAD BEEN BETTER LOCATED <input type="checkbox"/> YES, HAD THE CHILD NOT ACQUIRED AN INFECTION IN HOSPITAL <input type="checkbox"/> YES, IF THERE HAD BEEN NO WAITING PERIOD BEFORE EXAMINATIONS <input type="checkbox"/> YES, THE FOLLOWING CONDITIONS HAD BEEN MET _____ <input type="checkbox"/> NO _____	32	

DATE ____/____/____

PHYSICIAN'S SIGNATURE _____

ACTA

SUPPLEMENT 195 1961

PÆDIATRICA
SCANDINAVICA

CEREBRAL SYMPTOMS ^{DATA}
IN THE NEWBORN

BY INGRID THORN

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksell's Boktryckeri AB, Uppsala, Sweden without charge.)

131. Mollin, T. The Children of Swedish Nomad Lapland. A Study of their Health, Growth and Development. Sw. kr. 25.—1962
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135. J. Hansson, O. G. Generalist at his Retirement from the Professorship of Paediatrics at Karolinska Institute, June 30, 1962. Sw. kr. 25.—1962
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147. Astrand, P.-O., Lagerstedt, L., Eriksson, B. O., Karlberg, P., Nylander, L., Balke, D. and Thore, C. Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.—1963
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150. Moss, Peter Jehan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.—1963
151. Primitive Paediatrics in the Undergraduate Curriculum. Symposium held with the Collaboration of the World Health Organization at the X International Congress of Paediatrics, Lisbon, 1962. Edited by Be Valdemar. Sw. kr. 15.—1963
152. Hjern, Be and Nylander, Inger, Acute Liver Injuries in Children. Transfusion Therapy and Prognosis. Sw. kr. 15.—1964
153. Thore, Claes, Cardiomyopathy in Friedrich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.—1964
154. Hall, Berth, Mergolism on Newborns. A Clinical and Cytogenetic Study. Sw. kr. 30.—1964
155. Engström, Lars, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.—1964
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Price Sved kr 20.—

Cover printed in Sweden by Almqvist & Wiksell's Boktryckeri AB, Uppsala

**Cerebral Symptoms
in The Newborn**

Cerebral Symptoms in The Newborn

Diagnostic and
prognostic significance of symptoms
of presumed cerebral origin

By
Ingrid Thorn

Munksgaard

Copenhagen 1969

To Peter and Soren

Denne afhandling er af det lægevidenskabelige fakultet
ved Københavns universitet antaget til offentligt at
forsvares for den medicinske doktorgrad

København den 19 november 1968

M Faber

h. a. doc.

Preface

The present work was started at the Department of Paediatrics, The Copenhagen County Hospital in Gentofte. I thank the chief of the department, Dr med. *P W Børstrup* for inspiration and for much practical help.

The work continued during my appointment at the Department of Paediatrics of the University Hospital (Rigshospitalet). I thank Professor *P Plum* for experienced advice and for good working conditions.

Through the last stages of the work, while appointed to the Children's Hospital, Fuglebakken, I received much encouragement from the chief, Dr med. *H Andersen* for which I am grateful.

I also wish to express my thanks to the heads of the obstetrical departments of the University Hospital, Professor *E. Brandstrup* and Professor *D Trølle* for permission to use the records and for their interest.

I further thank Dr. *Inge Tygstrup* the Department of Pathology of the University Hospital, who willingly placed her meticulous pathological reports at my disposal.

For constant readiness in finding literature I wish to thank the staff at the University Library.

Not least my thanks are due to the children and their parents for kind participation in the examinations.

The translation has been made by Mrs. *B Damsgaard-Sørensen* medical secretary at the neurological department of the University Hospital, in cooperation with Miss *Kathleen Larkin*, medical secretary London, and the author. I thank both for quick and good work.

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Introduction

The diagnosis of neonatal disorders is fraught with great difficulty due to the non-specific reactions of the newborn to illness: one symptom may be caused by a variety of disorders, conversely one condition may present itself in a variety of ways, giving rise to multiple and severe symptoms, or only one symptom. Or it may be that a symptomless course will be followed by sudden death. Many unexpected diagnoses have been made on the autopsy table.

Because of the diagnostic difficulties, the incidence of perinatal cerebral damage is hard to establish and that of its sequelae even more so.

The challenge presented by these circumstances, as well as the severity of a number of the sequelae, are the motivation for the present study the purpose being an attempt to evaluate the specificity and prognostic significance of supposedly cerebral symptoms in the newborn.

CHAPTER I

Previous studies of cerebral symptoms in the newborn

The most reliable information concerning the symptomatology of intracranial disorders in the newborn is offered by authors correlating clinical observations with autopsy findings.

Previous studies of this kind have been based on limited series. *McNutt* (1885) examined 10 infants with intracranial haemorrhage. Nine had died within the first week of life, and the tenth when 22 days old. The clinical symptoms were not described in every case. It was emphasised that convulsions with haemorrhages over the convexity of the brain, were localized and accompanied by corresponding pareses, whereas they were generalized when the intracranial haemorrhages were found mainly in the base of the brain and around the cerebellum. Convulsions, however, were not necessarily present, and were especially rare with supratentorial haemorrhages. Among other inconsistent features were a refusal to nurse, cyanosis and irregular respiration.

Seltz, (1907) dealt with symptoms of increased intracranial pressure in 14 infants dying during the neonatal period. On clinical grounds he, too, distinguished between supra- and infratentorial haemorrhages. Patients with supratentorial haemorrhages, according to Seltz, were characterized by restlessness, crying and by a rigidity that was succeeded by flaccidity. Moreover the fontanelle was tense. Infants with infratentorial haemorrhages, on the other hand, were apathetic, suffered from respiratory disorders and cyanosis as well as progressive spinal symptoms: opisthotonus, rigidity and clonic convulsions. Seltz pointed out that the most severe cases of intracranial haemorrhage led to rapid death without preceding evidence of increased intracranial pressure. He also stated that cerebral oedema in the absence of haemorrhage might give rise to symptoms similar to those with cerebral haemorrhage.

Green (1914) presented a small series of patients with intracranial haemorrhage. He, too, stressed the absence of symptoms in several cases. In other patients he had found refusal to nurse, pallor and facial oedema as initial symptoms, which might be followed by more "classical" symptoms.

Esch (1916) found, like Seltz, that cerebral haemorrhage and oedema might present identical symptoms and that many cases—whether fatal or not—were symptomless. He was not able to distinguish clinically between supratentorial and infratentorial haemorrhage. He did, however distinguish between early (i.e. present at birth) and late (i.e. developing within the first 24 hours) symptoms. As an early symptom frequently leading to early death he stressed severe respiratory disorders. Many late symptoms were severe and their outcome often fatal.

Brady (1918) and Munro and Ewart (1922) had made observations similar to those of Seltz. Sidbury (1920) found a similar symptomatology failed, however to distinguish between supratentorial and infratentorial haemorrhage. Both Brady and Sidbury concluded that the diagnosis was extremely difficult, and that intracranial haemorrhage should be borne in mind whenever the clinical picture was unclear.

A major study of autopsy material was presented by Heidler (1927) consisting of 131 neonates dying from cerebellar tentorial tear. In most cases he reported only apathy and feeble cry or even a complete absence of symptoms, particularly in premature infants. Irregular respiration, cyanosis and finally convulsions were noted. He was unable to distinguish between supratentorial and infratentorial haemorrhage. In 20 patients with leptomeningeal haemorrhage, five intraventricular and five intracerebral, he found a symptomatology similar to that seen in tentorial tear. In six patients with brain contusion, oedema and hyperaemia the clinical features were pallor, restlessness, irregular respiration and convulsions.

Dollinger (1927) discussed the difficulty of differential diagnosis due to "the monotony of the clinical pictures" in different conditions, some of them extracerebral, and the diversity of clinical manifestations of the individual diseases. He experienced no diagnostic difficulty when an intracranial haemorrhage gave rise to what has later been referred to as Dollinger's "large picture" with severe irritative or parietic symptoms. He stressed, however that in a great many cases of intracranial haemorrhage only the "small picture" was present, including debility and nutritional and pulmonary disorders. With small haemorrhages in the medulla he found respiratory difficulties. Cyanosis was found to be associated with respiratory disorders or small haemorrhages in the vasomotor centre. Convulsions were frequent, though they might be absent even with extensive haemorrhages. This was true also with disturbances of consciousness. He considered rigidity to be a spinal symptom.

Cleis (1929) was concerned with the problems of differential diagnosis in premature infants. In 36 infants, who died in the neonatal period, he found intracranial haemorrhage in 21 and none in the remainder. In the two groups there were differences in symptomatology in that cyanotic attacks were seen

only in intratentorial haemorrhage, and apathy was more pronounced in intracranial haemorrhage. Tremor was as frequent in intracranial haemorrhage as in extracerebral conditions (atelectasis or infections). Convulsions were seen in only three of the newborn who died, none showing cerebral damage.

Catel (1932) and *Liebe* (1940) established the diagnosis of intracranial haemorrhage on the basis of differences in the bilirubin concentration in blood and spinal fluid and found the validity of this method confirmed by autopsy findings in 34 and 68 infants respectively dying in the neonatal period. Both authors observed that some of the infants with intracranial haemorrhage failed to present any symptoms, and in patients with no intracranial haemorrhage similar symptoms might be observed as in those who had. They found, however that infants with intracranial haemorrhage frequently developed more symptoms but not enough to enable a diagnostic conclusion to be reached. *Liebe* regarded cyanosis, convulsions, refusal to nurse and decreased activity as non-specific symptoms, while delayed initial crying and intermittent loss of consciousness were more likely to be cerebral symptoms.

Rydberg (1932) observed that severe cerebral symptoms usually occurred after a symptomfree interval of hours or days poor nursing and apathy or intermittent or constant cyanosis as initial symptoms were followed by tremor rigidity convulsions, irregular respiration and high-pitched cry. All symptoms, however, were inconsistent. With a full clinical picture they were considered almost pathognomonic of intracranial haemorrhage. Such a picture was observed in 34 infants who died in the neonatal period. Six of these had no intracranial haemorrhage, but prominent degenerative tissue alterations were present in the brain. *Rydberg* further described an uncharacteristic picture which also developed after a symptomfree interval and was seen in a variety of diseases. It consisted of irregular respiration and cyanosis. *Rydberg* concluded that a clinical diagnosis in such cases was impossible.

Grulee (1936) reached practically the same conclusion in his study of 166 infants dying in the neonatal period, and in whom intracranial haemorrhage occurred in 20. He found that convulsions in the newborn could be a symptom of almost any disease.

Craig (1938) gave a detailed description of clinical observations and autopsy findings in 126 newborn infants dying of intracranial haemorrhage. The series was classified according to the site of the haemorrhage. As well as demonstrating aetiological differences within the respective categories he concluded, subarachnoidal haemorrhage gave usually rise either to uncharacteristic symptoms or to none at all (36 patients). Subdural haemorrhage, the most common finding (62 patients) often associated with tentorial tear

was characterized by a good period followed by an irritative stage and eventually by a depressive stage, whereas intraventricular haemorrhage followed a brief course with death concluding a sudden onset of severe symptoms, frequently associated with terminal hyperpyrexia. With haemorrhage into the brain substance the course was often lengthy with progressive weight loss, mental restlessness and pronounced physical weakness. More over it was stressed that convulsions were indicative of an intracranial process only in the presence of other symptoms of probable cerebral origin such as shrill cry or a bulging fontanelle. In the case of subdural haemorrhage convulsions were often more pronounced and of longer duration than in other forms of intracranial haemorrhage. Rigidity and opisthotonus were more indicative of intraventricular and subdural intratentorial haemorrhage; in the latter case this was usually associated with cyanosis in contrast to the former.

Bowd, Butler and Spector (1956) published a survey of 211 consecutive neonatal deaths of mature and premature infants. The principal causes of death were: 1) intraventricular haemorrhage in 10 per cent, 2) intracranial birth injury in 18 per cent, 3) a "pulmonary syndrome" in 27 per cent, 4) pneumonia in 12 per cent, 5) various diseases including malformations in 33 per cent. One or more of the following groups of symptoms were present in all the first four groups: 1) poor condition at birth, i.e. flaccidity and poor reaction to stimuli, cyanosis and respiratory irregularities—as seen in over half the cases in all four groups, 2) respiratory disorders in the form of rapid, irregular breathing, gradually with periods of apnoea, and intermittent or permanent cyanosis. These features were present in all the patients. 3) Irritative cerebral symptoms: convulsions, often associated with abnormal wakefulness, restlessness, irritability, high-pitched cry and changes in tone. These last symptoms were seldom encountered in the absence of convulsions. Only 24 per cent of these patients had intracranial lesions and 63 per cent had pulmonary changes only—Just over one third of the patients with "pulmonary syndrome" had irritative cerebral symptoms, and this also applied to the patients with intraventricular haemorrhage. One quarter of the patients with intracranial birth injury died within the first hour of life. Among the mature patients who lived longer the majority had irritative cerebral symptoms compared with less than half in the premature. It was concluded that the clinical picture was of no appreciable significance in the differential diagnosis.

Millingworth (1957) studied the significance of cyanotic attacks in the differential diagnosis in 170 newborn infants, 82, or 48 per cent of whom died neonatally. 36 per cent of those had severe atelectases and 33 per cent had marked intracranial haemorrhage. Almost identical findings were present in newborn infants dying neonatally without having exhibited cyanotic attacks. Nineteen of those who did have cyanotic attacks also had convulsions. In

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eleven cases autopsy revealed intracranial abnormalities (haemorrhage or oedema) and in four atelectasis or congenital heart disease were disclosed.

Ahvenainen (1956 1957 1958 and 1959) carried out meticulous studies of the clinical and pathological findings in small groups of infants with either pulmonary or intracranial disorders who died in the neonatal period. He reported that cyanosis was among the most frequent symptoms in all groups. He also found that oxygen therapy often had no effect on cyanosis caused by cerebral damage. Respiratory disorders were also common, and he considered irregular respiration to be the most reliable respiratory symptom in the diagnosis of intracranial conditions. Unconsciousness and flaccidity were more frequent than convulsions and rigidity in cerebral disorders. Though rare, all the cerebral symptoms might be present in pulmonary disorders; convulsions were observed only in the terminal stage. *Ahvenainen* felt that the presence of two cerebral symptoms in any one patient made the diagnosis of intracranial disease more certain than one cerebral symptom. He pointed out that pulmonary complications were frequent in intracranial conditions and that their presence modified the cerebral symptoms, thus making the diagnosis even more difficult. He demonstrated that none of the features mentioned were common to all cases.

Peterman (1946) reported cerebral birth injury to be the cause of convulsions in 68 per cent of 176 infants with convulsions during the first month of life. Among other causes he mentioned acute infections within or outside the central nervous system, hydrocephalus, cerebral agenesis and congenital heart disease. In 7 per cent of the cases the origin remained unknown.

Craig (1960) examined 374 infants with convulsions. 158 or 42 per cent died neonatally. Postmortem examinations revealed a cerebral aetiology in 78 per cent. In 16 per cent only extracerebral disease was found, and in 6 per cent no cause could be discovered. He felt that convulsions could be distinguished to a certain extent according to aetiology. Moreover he stated that severe cases of convulsion were remarkably rare in premature infants.

Dekaban in his book "Neurology of Infancy" (1959) described an essentially similar symptomatology in intracranial haemorrhage of varying localization as stated by *Craig* (1938).

In summarising, it may be concluded that the diagnosis of intracranial disease in the neonatal period has been considered difficult and has usually been established from the presence of one or more of the following symptoms: cyanosis, respiratory disorders, abnormalities in consciousness and tone, convulsions and refusal to nurse. The presence of several symptoms ensures a fairly accurate diagnosis. However where few symptoms are present—as is frequently the case—the diagnosis is extremely uncertain. It would appear that no one symptom can be said to be specifically cerebral.

Previous studies on the prognosis of intracranial disorders in the newborn and the prognostic significance of neonatal symptoms

Brady (1918) found that among nine patients with severe cerebral symptoms four had died in the neonatal period from intracranial haemorrhage, three had survived, but with serious cerebral sequelae (spasticity and convulsions) and two had undergone a perfectly normal development.

Heidler (1927) published a follow-up study of fourteen out of 22 patients who had survived neonatal disease. All had had convulsions and several additional cerebral symptoms. At the age of three years 12 were found to be practically normal, two had hemiplegia, seizures and mental defects.

Dollinger (1927) found the prognosis of intracranial birth injury to be graver the earlier in onset, the longer duration and the more severe and numerous were the symptoms. Convulsions lasting longer than one day were invariably considered an ominous sign. The previously mentioned "large picture" implied a higher mortality rate, the "small picture" a lower mortality rate, though a higher morbidity.

Naujoks (1928) located 24 children who had survived a neonatal period characterized by severe cerebral symptoms. Nine, ranging from two to twenty years of age, were found to be perfectly normal, four had minor defects (macrocephaly "nervous stereotype" and speech disorders) which could not with certainty be related to birth injury. An unspecified number had died within the first year of life, several had mental defects, seizures and pareses of the legs, but no cases of Little's disease were found. No differences in neonatal symptomatology were demonstrated between those who were normal and those who had sequelae. However this had not been the object of the investigation.

Muro (1928 and 1930) analysed the symptoms in 117 newborn infants with suspected intracranial damage. Ignoring symptoms that had not been present in at least 10 patients, he distinguished between "major" symptoms, viz. those present in approximately one-half to well over two-thirds of the subjects, and "minor" symptoms, observed in around one-tenth to one-quarter only. This grouping had no relation to the prognostic significance of these symptoms, and severe symptoms were present in both groups. Cyanosis, which was common, was compatible with less than a 50 per-cent chance of survival, even less if associated with asphyxia or respiratory distress. With hypotonicity which was also very frequent, the rate of survival was more than 50 per cent. Irritative symptoms were rare (one-quarter of the patients) with 70 per-cent chance of survival. Among the rare symptoms, asphyxia, pallor and flaccidity implied a poor prognosis. asphyxia was par

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In summarising, it may be concluded that the diagnosis of intracranial disease in the neonatal period has been considered difficult and has usually been established from the presence of one or more of the following symptoms: cyanosis, respiratory disorders, abnormalities in consciousness and tone, convulsions and refusal to nurse. The presence of several symptoms ensures a fairly accurate diagnosis. However where few symptoms are present—as is frequently the case—the diagnosis is extremely uncertain. It would appear that no one symptom can be said to be specifically cerebral.

Previous studies on the prognosis of intracranial disorders in the newborn and the prognostic significance of neonatal symptoms

Brady (1918) found that among nine patients with severe cerebral symptoms four had died in the neonatal period from intracranial haemorrhage, three had survived, but with serious cerebral sequelae (spasticity and convulsions) and two had undergone a perfectly normal development.

Heldler (1927) published a follow-up study of fourteen out of 22 patients who had survived neonatal disease. All had had convulsions and several additional cerebral symptoms. At the age of three years 12 were found to be practically normal, two had hemiplegia, seizures and mental defects.

Dollinger (1927) found the prognosis of intracranial birth injury to be graver the earlier in onset, the longer duration and the more severe and numerous were the symptoms. Convulsions lasting longer than one day were invariably considered an ominous sign. The previously mentioned "large picture" implied a higher mortality rate, the "small picture" a lower mortality rate, though a higher morbidity.

Naufels (1928) located 24 children who had survived a neonatal period characterized by severe cerebral symptoms. Nine, ranging from two to twenty years of age, were found to be perfectly normal, four had minor defects (macrocephaly, nervous stercotype and speech disorders) which could not with certainty be related to birth injury. An unspecified number had died within the first year of life; several had mental defects, seizures and paresthesia of the legs, but no cases of Little's disease were found. No differences in neonatal symptomatology were demonstrated between those who were normal and those who had sequelae. However this had not been the object of the investigation.

Aicardi (1928 and 1930) analysed the symptoms in 117 newborn infants with suspected intracranial damage. Ignoring symptoms that had not been present in at least 10 patients, he distinguished between "major" symptoms, viz. those present in approximately one-half to well over two-thirds of the subjects, and "minor" symptoms, observed in around one-tenth to one-quarter only. This grouping had no relation to the prognostic significance of these symptoms, and severe symptoms were present in both groups. Cyanosis, which was common, was compatible with less than a 50 per-cent chance of survival, even less if associated with asphyxia or respiratory distress. With hypotonicity which was also very frequent, the rate of survival was more than 50 per cent. Irritative symptoms were rare (one-quarter of the patients) with 70 per-cent chance of survival. Among the rare symptoms, asphyxia, pallor and flaccidity implied a poor prognosis, asphyxia was par

eleven cases autopsy revealed intracranial abnormalities (haemorrhage or oedema) and in four atelectasis or congenital heart disease were disclosed.

Ahvenainen (1956 1957 1958 and 1959) carried out meticulous studies of the clinical and pathological findings in small groups of infants with either pulmonary or intracranial disorders, who died in the neonatal period. He reported that cyanosis was among the most frequent symptoms in all groups. He also found that oxygen therapy often had no effect on cyanosis caused by cerebral damage. Respiratory disorders were also common, and he considered irregular respiration to be the most reliable respiratory symptom in the diagnosis of intracranial conditions. Unconsciousness and flaccidity were more frequent than convulsions and rigidity in cerebral disorders. Though rare, all the cerebral symptoms might be present in pulmonary disorders convulsions were observed only in the terminal stage. Ahvenainen felt that the presence of two cerebral symptoms in any one patient made the diagnosis of intracranial disease more certain than one cerebral symptom. He pointed out that pulmonary complications were frequent in intracranial conditions and that their presence modified the cerebral symptoms, thus making the diagnosis even more difficult. He demonstrated that none of the features mentioned were common to all cases.

Peterman (1946) reported cerebral birth injury to be the cause of convulsions in 68 per cent of 176 infants with convulsions during the first month of life. Among other causes he mentioned acute infections within or outside the central nervous system, hydrocephalus, cerebral agenesis and congenital heart disease. In 7 per cent of the cases the origin remained unknown.

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had been practically identical in the neonatal period (cf. page 14) The follow-up also failed to reveal any differences. Three, or 21 per cent, of Lieke's fourteen patients with intracranial haemorrhage and sixteen (24 per cent) of 68 patients without intracranial haemorrhage had severe cerebral sequelae. The corresponding figures in Caste's somewhat smaller series were 33 and 25 per cent, respectively.

Craig (1950) published an extensive and detailed study on 593 children with neonatal intracranial irritation. He had excluded children with morbus haemolyticus neonatorum, severe persistent atelectasis and malformations. The series was divided into five groups according to neonatal symptom groups in decreasing degrees of severity. All the children had been seen at the age of six months. 12 patients were excluded because of microcephaly and handicaps that might be of hereditary developmental origin or acquired at a later date. 14 per cent were not re-examined after 6 months of age, 6 per cent died of unknown causes, 80 per cent were followed up until the age of one year 71 per cent to the age of three years and 52 per cent beyond five years of age. In the entire material severe cerebral sequelae were present in 56, or 9 per cent. In the group with severe neonatal symptoms (53 patients) sequelae were found in 21 per cent, in the group with pronounced symptoms (104 patients) in 10 per cent, in the group with moderate symptoms (238 patients) in 8 per cent, of those with mild symptoms (187 patients) 7 per cent had sequelae, and for those with delayed symptoms (11 patients) the rate was 36 per cent.—The patients with severe sequelae were fairly evenly distributed throughout the symptomatological groups.—Craig concluded that there was no correlation between neonatal symptoms and later development except in cases with delayed neonatal symptoms, which gave a poor prognosis. The outlook for immediate survival was grim in the presence of collapse, gasping and irregular respiration that was not corrected within hours, particularly when associated with cyanosis. A marked difference in the symptomatology of premature and mature infants was demonstrated by Craig in so far as the premature only rarely showed the violent clinical pictures in the neonatal period. If convulsions occurred in the premature, the prognosis for survival was grave. However the late prognosis was no worse for premature patients than for mature. It was suggested that it was the duration of the neonatal symptoms rather than their severity that was prognostically significant.

Roudinesco Tardieu, Willwald and Trelet (1951) followed up throughout a period of three years 54 out of 62 children who had been admitted to hospital in the neonatal period because of suspected cerebral disease. 60 per cent developed normally 25 per cent had permanent cerebral sequelae of varying degrees and 15 per cent seemed to have been only temporarily retarded. Symptoms with grave prognostic implications were in this study so-

icularly relevant to late sequelae. Common symptoms were also feeble crying, poor nursing, apathy respiratory disorders and a bulging fontanelle. Half the 117 patients died in the neonatal period. 48 of the 58 survivors were included in the follow-up at ages varying from 2½ to 7 years. 34 (70 per cent) were found to be normal and 7 (14 per cent) had serious cerebral sequelae. Of these four had died an additional seven deaths were due to extracranial causes. Munro did not differentiate the neonatal symptomatology in the various groups of survivors.

Fleming and Morton (1930) In a comparable study investigated a series of 103 patients with neonatal symptoms interpreted as cerebral in origin. They too found that about half the patients had died. Out of 53 survivors 33 were examined at the age of at least one year. Of these 28 or 85 per cent, were normal and 5 or 15 per cent, had severe cerebral defects. At least seven were reported to have died after the neonatal period, however the cause of death could not be established. Fleming found no differences in the neonatal symptomatology between those who were eventually found to be normal and those who had sequelae. He concluded that it was impossible to predict the outcome of the survivors. Cyanotic attacks and convulsions were considered to be specific cerebral symptoms. Convulsions occurred in about half the patients their chance of survival equalled that of Munro's patients with irritative cerebral symptoms.

Rydberg (1932) reported a graver prognosis in 48 children surviving severe neonatal symptoms. One third developed severe cerebral sequelae, approximately a further third had obvious cerebral symptoms. The final prognosis of the latter however was uncertain. But one-third were normal or practically normal. The age range of the children at follow-up was three to eighteen years. No differences in symptomatology could be demonstrated in the respective groups.

Fischer (1938) investigated a series similar to that of *Heldler's (1927)* comprising 24 children who had had convulsions and various other cerebral symptoms in the neonatal period. 18 were traced and re-examined. The outlook was worse than in *Heldler's* series, with five deaths from cerebral causes presumably related to the neonatal disease. Five had varying degrees of mental handicap. Two of these also had convulsions, two had speech disorders and one had impaired hearing. Eight, or 44 per cent, were found to be normal.

Catell (1933) and *Liebe (1940)* who based the diagnosis of intracranial haemorrhage primarily on the relationship between bilirubin levels in blood and spinal fluid carried out follow-up studies on two series of 26 and 82 children, respectively who had survived neonatal disease. Both series included children in whom intracranial haemorrhage had been diagnosed, and others in whom the diagnosis had been disproved. Clinically the two groups

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vere primary asphyxia and flaccidity (which was rare) cyanosis was a somewhat less, though still serious prognostic sign, whereas hypertonicity was found to be of minor importance, and convulsions even less.

Hellström and Jonsson (1953) investigated 85 full term infants, who had been admitted to a paediatric ward either because of asphyxia or with manifest signs of oxygen deficit or evidence of intracranial haemorrhage. 18 died in the neonatal period of these 15 had intracranial haemorrhage. Four died later of unknown causes. The remaining 63 were examined at ages ranging from 2 to 9 years. 28 per cent had severe sequelae. Not all these children had shown clinical symptoms in the neonatal period. Cyanosis, which occurred in 40 per cent, and hypotonicity present in 17 per cent, were found to have no significance in the late prognosis. Convulsions and rigidity occurring in 15 per cent, seemed to imply a poor prognosis, since about 80 per cent of the patients in whom these symptoms were observed later developed severe sequelae. In contrast, only 20 per cent of the children who had had none of these symptoms were found to have sequelae.

Znamenacek, Horsky, Jirsova and Melichar (1957) followed up 202 children having had evidence of perinatal injury until the age of 3 years. A large majority (167) had presented symptoms only within the first day of life (ascribed to postnatal aspiration, asphyxia—often severe—anaesthesia or traumatic shock). The fact that all these children later developed normally implies that symptoms lasting up to 24 hours may be considered unimportant.—26 had symptoms of up to ten days duration. The symptoms were graduated as mild (rigidity, transient irritability, opisthotonus and tremor in mature infants and brief spells of apnoea and cyanosis in the premature) and severe (pronounced depressive and irritative symptoms). The mild symptoms left no sequelae; in the severe cases sequelae in the form of retarded development were found in 5 out of 15 cases. Great prognostic significance was ascribed to convulsions, unconsciousness and insufficient response to stimuli in the full term infants and, in the premature, their failure to maintain normal breathing.

Gross (1958) in a follow-up study of 136 children presenting various cerebral symptoms neonatally found that 6 per cent had died of unknown causes, 11 per cent had serious cerebral sequelae, and 83 per cent were perfectly normal. The ages at follow-up were from one to seven years and the follow-up percentage was 58. *Gross* found that cerebral symptoms were not necessarily unfavourable prognostic signs.

Burke (1954) examined a series of 46 newborn infants with special regard to the prognostic significance of convulsions. 18 or 38 per cent, died in the neonatal period. The prognosis for immediate survival appeared to be appreciably worse in the premature, with six out of 10 patients dying, while only 12 out of 36 mature infants had died. Among the survivors, 5 (19

per cent) developed severe cerebral sequelae, comparable to the rate found by Heldler (1927)

Bound, Butler and Spector (1956) found convulsions to be a grave prognostic sign for immediate survival, particularly in the premature, in whom, as mentioned on page 15 this symptom is rare. Out of 24 full-term infants with convulsions 42 per cent died neonatally compared with 79 per cent of 33 premature.

Craig (1960) in his paper on convulsions during the first 10 days of life, reported a follow-up study of 141 out of 152 children with neonatal convulsions of probable cerebral origin compared with 488 children who had had no convulsions, but other evidence of postnatal anoxia. The age at follow-up was well over three years. He found a higher incidence of severe cerebral sequelae (8 per cent) in the group with convulsions than in the group with none (3 per cent). The duration of the convulsions apparently had no effect on the outcome.

Harlem and Oseid (1961) attached great importance to convulsions, especially when occurring repeatedly during the neonatal period. They followed-up 189 children who had various symptoms of cerebral irritation (immediate mortality rate 50 per cent) and found sequelae in 33 per cent.

Ford (1960) pointed out that little is known of the anatomical conditions in the brains of children surviving a perinatal injury. He felt that numerous disorders have been ascribed to birth injury without conclusive evidence and he emphasized that even those best able to express an opinion on the subject appear to disagree.

To sum up, one must admit that there is basis for dispute. There is, however general agreement that a prognosis based on clinical observations only is precarious, indeed. Opinions differ also concerning the relative prognostic significance of individual symptoms, and to a lesser degree as to the future development of children with supposed cerebral symptoms in the neonatal period.

Recent years have brought forth new and more systematic methods of investigation. In 1953 Apgar presented her method for evaluating the condition of newborn infants within minutes of birth. Her scoring system, by which heartbeat, respiration, muscle tone, reflex irritability and colour were recorded and classified, the highest score indicating the optimal condition, has been widely used and has proved its validity. It has revealed a close correlation between low scores and high neonatal mortality especially within the first two days of life. The correlation was more apparent with low scores at five minutes than at one minute after birth, and the highest mortality was found in infants with low birth weights and low scores (Drage Kennedy and Scherer 1964). Apgar's system has also proved of prognostic value with regard to later morbidity. A considerable number of neurological defects

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CHAPTER II

Material and method

The present series consists of 291 children who, in the neonatal period, have been admitted to a paediatric ward because of symptoms suggesting cerebral damage.

The infants had been admitted to the Department of Paediatrics (DPGe) at Copenhagen County Hospital in Gentofte (KASGe) over a ten-year period (1946-1955). Although the neonatal period is defined here as the first week of life, a number of patients who were admitted during their second week have been included, they had, however, exhibited symptoms during the first week of life.

The investigation is based on the hospital records, and the patients were selected as follows: All cases that were registered under a diagnosis of intracranial haemorrhage, a total of 156 have been included. A review of the records revealed that the diagnosis had been based on the following symptoms, occurring in varying combinations and numbers, seldom alone, in the following order of frequency:

- 1) cyanosis, mostly attackwise, though in several cases constant. (Peripherical cyanosis has been disregarded)
- 2) Respiratory disorders consisting of irregular often difficult, grunting respiration, occasionally with periodic apnoea.
- 3) hypotonicity often combined with apathy
- 4) Convulsions.
- 5) Tremor
- 6) Restlessness and irritability
- 7) Rigidity

It was apparent from the records that the diagnosis in several cases had been based on 1-3 of the following symptoms. cyanosis, respiratory disorders and apathy none of which can be considered specifically cerebral in nature.

The file was therefore searched for diagnoses that either a) suggested cerebral damage (difficult delivery skull fracture, asphyxia neonatorum), or

were found at the age of one year in children with low scores, again most apparent with five minutes low scores, and the worst prognosis was found in small premature infants with low scores (*Drage and Berendes 1966*). Their results have been published as part of a comprehensive collaborative study on cerebral palsy mental deficiency and other neurological disorders in childhood.

Graham Matarazzo and Caldwell (1956) published another method for the evaluation of the newborn, which they used in 265 newborn infants with no perinatal complications and in 81 with anoxic or cerebral complications, and correlated with re-examination of the children at the age of 3 years (*Graham Ernhart Thurston and Craft 1962*). A higher incidence of sequelae was revealed in those children who had been suspected of cerebral defects neonatally but there was no consistent parallel between the neonatal tests and the later condition, although certain significant correlations were established.

A very elaborate method for neurological examination on the basis of observation of the development of the central nervous system and its mode of reaction in childhood has been developed by *André Thomas and Saint-Anne Dargassies (1952)* *Prechil (1956 and 1964)* *Prechil and Dijkstra (1959)*. The object has been the disclosure of minor brain damage in the neonatal period. The prognostic significance of the abnormal neurological findings in neonates was confirmed by follow up studies (*Prechil 1960* *Dijkstra 1960* *Snithells 1961* and *Saint Anne Dargassies 1962*) which disclosed significantly more neurological disorders, especially behaviour deviations, in the groups with abnormalities in the neonatal period as compared with normal neonates. These methods are extremely time-consuming and require great experience, if errors of judgment are to be avoided. This has been stressed by *Illingworth (1960)* among others, who anticipated the risk of demonstrating in the newborn more and more signs that will eventually disappear. *Paine (1960)* also questioned the prognostic value of some of these elaborate investigations and stressed his point again (*Donovan Coues and Paine 1962*) in a paper on 192 full-term infants observed at birth and again at the age of one year. He concluded that conventional neurological signs and infantile postural automatisms were of limited prognostic value, even though "minimal brain damage" could not be expected to be disclosed at the age of one year. However the investigations were found to be useful in the neonatal diagnosis—The methods are widely used at present, where large prospective studies are in progress, and the final judgment must be withheld until the completion of a long-term follow-up study.

Follow-up examination

At the follow-up examination the mothers were interviewed in order to obtain supplementary data concerning pregnancy and delivery and a detailed history of the children was taken. Special emphasis was placed on general condition and growth during the first years of life as well as later. An attempt was made to assess whether the motor and mental development of the patients had differed from the assumed average. With older normal children it could be difficult to assess the exact time at which a child had mastered such important functions as walking, talking or toilet habits. Had development not been unsatisfactory information was generally more accurate.

In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older the mothers were asked at what age the children had begun school and what progress they had made there.

When behaviour problems were present, the nature of the defect was explored as far as possible, and an attempt was made to disclose possible causative factors in the child's environment.

If psychological testing had been carried out, either because of a suspected mental defect or specific difficulties with learning or behaviour problems, reports were obtained from doctors or psychologists. In only a few cases had psychological tests been brought about with the prime object of assessing whether a so-called organic element was present or not.

During the examination of the child no proper psychological tests were made however a clinical evaluation was made, based on conversation with the child and observation during the examination itself, which usually lasted for about an hour.

Electroencephalography (EEG) was performed wherever possible in cases where deviations of behaviour were suspected to be of organic origin. The recordings were performed and interpreted by the physicians of the EEG-laboratory at the University Clinic of Paediatrics.

A number of the children, who had a present or past history of various types of seizures, were, when possible, examined by EEG. If this had not already been done. If EEG studies had already been made, the reports were obtained.

In the same way data on previous examinations were obtained, if the child had been seen by specialists because of defects of vision, hearing or speech, or if a disorder of assumed cerebral origin had led to admission to hospital or out-patient treatment.

Finally a general physical and neurological examination was performed.

b) suggested the presence of the above-mentioned non specific symptoms (pulmonary atelectasis, aspiration into the lungs or congenital debility) From these two groups have been selected those infants who presented at least two of the non-specific or at least one of the presumably specific symptoms, from a) 31 from b) 104 patients.

Infants who might have exhibited similar symptoms, but were registered under other definite diagnoses, such as proven heart disease or hiatus hernia, were omitted. So were patients with icterus neonatorum with or without blood-group-incompatibility.

As with any other study based on records that have not been written with a specific scientific objective in mind, to a certain extent the present material must be considered unreliable. One should be able to rely upon notes stating the presence or absence of a symptom however one is at a loss if the symptom is not mentioned at all.

From this point, when a symptom is said to have been absent, in some instances this may have been stated explicitly in other cases, however the symptom may not have been mentioned in the notes. No such distinction has been made in the analysis of the material on the assumption that a serious symptom would have been recorded, had it been present.

Information about pregnancy and delivery is more unsatisfactory since all the infants had been delivered at a place other than the KASGe (at home, in a private clinic or at another hospital). The data accompanying the child on admission was often scanty and additional information was not always obtainable.

Cases in which a given procedure has not been mentioned and those where it was explicitly stated that the procedure had not been applied have therefore not been listed together.

The following information has been extracted from the records.

- 1) *Data on the mother* Age, parity, matrimonial status, condition during pregnancy and complications, if any.
- 2) *Data on the delivery* Course and duration, complications, use of labour stimulating methods, morphine, or forceps.
- 3) *Data on the patient*. If asphyxia occurred its duration as well as the extent and method of attempted resuscitation. (In the present study asphyxia is defined as delayed establishment of spontaneous respiration after birth). The age of the child on admission to the ward and the duration of the admission. The symptoms that caused the admission or developed following admission. The time of onset and the duration of these symptoms. The therapy applied. The condition of the infant at discharge. Where death occurred, extracts from the autopsy report were obtained.

Follow-up examination

At the follow-up examination the mothers were interviewed in order to obtain supplementary data concerning pregnancy and delivery and a detailed history of the children was taken. Special emphasis was placed on general condition and growth during the first years of life as well as later. An attempt was made to assess whether the motor and mental development of the patients had differed from the assumed average. With older normal children it could be difficult to assess the exact time at which a child had mastered such important functions as walking, talking or toilet habits. Had development not been unsatisfactory information was generally more accurate.

In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older, the mothers were asked at what age the children had begun school and what progress they had made there.

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In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older the mothers were asked at what age the children had begun school and what progress they had made there.

When behaviour problems were present, the nature of the defect was explored as far as possible, and an attempt was made to disclose possible causative factors in the child's environment.

If psychological testing had been carried out, either because of a suspected mental defect or specific difficulties with learning or behaviour problems, reports were obtained from doctors or psychologists. In only a few cases had psychological tests been brought about with the prime object of assessing whether a so-called organic element was present or not.

During the examination of the child no proper psychological tests were made; however a clinical evaluation was made, based on conversation with the child and observation during the examination itself, which usually lasted for about an hour.

Electroencephalography (EEG) was performed wherever possible in cases where deviations of behaviour were suspected to be of organic origin. The recordings were performed and interpreted by the physicians of the EEG-laboratory at the University Clinic of Paediatrics.

A number of the children, who had a present or past history of various types of seizures, were, when possible, examined by EEG if this had not already been done. If EEG studies had already been made, the reports were obtained.

In the same way data on previous examinations were obtained, if the child had been seen by specialists because of defects of vision, hearing or speech, or if a disorder of assumed cerebral origin had led to admission to hospital or out-patient treatment.

Finally a general physical and neurological examination was performed.

The follow-up study was begun at the end of 1958 at that time the children were thus between three and thirteen years old.

Of the total of 291 children 123 had died during their first admission to hospital. Autopsy had been performed in all cases but one (owing to refusal by the parents) and this case has been excluded from the material.

168 patients survived the neonatal period. Of these 15 had to be excluded, four could not be traced four had left the country and their addresses were unobtainable the parents of five refused to cooperate and data about these children were unobtainable in any other way one infant had died with the mother from carbon monoxide poisoning. The death certificate carried no additional information. One child who had athetosis, was excluded because she was later found to have had prolonged jaundice due to blood-group-incompatibility between mother and child.

12 infants, who had died at a later date, have been included in the material since there was ample information about their subsequent history in seven cases autopsy reports were available. In the case of six of the survivors it was possible to obtain written information only

The remaining children have been examined either at the DPGs following written invitation, in their homes or at the institutions in which they had been placed.

This gives a follow-up percentage, among the survivors, of 91. For the entire series, now reduced to 275 cases, the percentage is 95.

The neonatal symptoms

As mentioned above, the neonatal symptoms related to cerebral damage or cerebral irritation were as follows: cyanosis, respiratory disorders, hypotonicity, convulsions, tremor, irritability and rigidity.

Fig. 1 a shows the incidence of each of the neonatal symptoms. It will be seen that three-quarters of the patients had cyanosis, well over one-half had respiratory abnormalities and apathy, less than a quarter had convulsions and less than one-fifth had tremor, irritability and rigidity. There was an average of 2.5 symptoms per patient. Because of the origin of the material it should be permissible to regard these figures as minimum numbers.

37 or 13 per cent of the patients had exhibited only one symptom. 22 had cyanosis, 8 hypotonicity, 3 respiratory disorders, 2 convulsions and 2 irritability. The remainder had exhibited symptoms in varying combinations.

The rate of prematurity in the total material was very high. 96 infants, or 35 per cent, had a birth weight (BW) below 2500 grams. The available information on the length of gestation did not permit classification and the distinction between maturity and prematurity therefore had to be based on

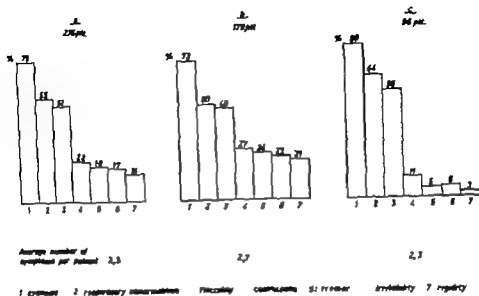


Fig. 1

Incidence of the neonatal symptoms: a) in the total material, b) in patients with BWs over 2500 grams and c) in patients with BWs below 2500 grams.

the BW alone.—As the premature might be expected to show a different pattern from that of the mature, the following analysis of the material is made also for the two weight groups separately.

Fig. 1 b and c illustrate the incidence of neonatal symptoms in mature and premature patients, respectively. It reveals a trend towards a higher incidence of cyanosis, respiratory disorders and flaccidity in the premature and a somewhat more pronounced tendency towards higher occurrence of convulsions, tremor, irritability and rigidity in the mature. Moreover there is a faint tendency for the mature to exhibit more symptoms than the premature: respectively 2.7 and 2.3 symptoms per patient.

Results of the follow-up

Of the 75 patients 44 per cent had died during the neonatal period, 11 per cent developed severe cerebral defects, 9 per cent had minor cerebral sequelae; 11 per cent, though essentially normal, had various minor abnormalities that, with a degree of certainty could be traced to the neonatal

The diagnoses of each group will be dealt with in details as follows.

1 Patients dying in the neonatal period

As mentioned above, autopsy including brain section, had been performed on all 122 patients. The studies were performed in the Department of Pathology of the KASGe. In Table 1 the principal findings are listed for the entire group, as well as for mature and premature patients.

Atelectasis was the most frequent finding and, as might be expected, more frequent in the premature. In all cases there were widespread pulmonary changes. Next in frequency were intracranial haemorrhages, somewhat commoner in the mature than in the premature. Tentorial tear was the pre dominant brain lesion in both weight groups, though much more frequent

TABLE 1
Principal autopsy findings in 122 patients dying in the neonatal period

	BW > 2500 gm 55 pat.	BW < 2500 gm 67 pat.	Total 122 pat.
Pulmonary atelectasis	75 %	88 %	81 %
Intracranial haemorrhage	73 %	63 %	67 %
Tentorial tear	64 %	48 %	55 %
Rupture of falx	2 %	3 %	2 %
Intraventric. haemorrhage	5 %	6 %	6 %
Rupture of sagittal sinus	2 %	0	1 %
Subdural haemorrhage	4 %	3 %	3 %
Subarachnoidal haemorrhage	4 %	2 %	2 %
Meningeal haemorrhage	13 %	10 %	11 %
Cerebral oedema	42 %	37 %	39 %
Meningeal oedema	70 %	13 %	16 %

TABLE 2
Combinations of main causes of death found at autopsy in 122 patients dying in the neonatal period

	BW > 2500 gm 55 pat.	BW < 2500 gm 67 pat.	Total 122 pat.
Pulmonary atelectasis			
Normal brain (20 patients)	9 %	22 %	16 %
Pulmonary atelectasis			
Cerebral oedema (19 patients)	16 %	15 %	15 %
Pulmonary atelectasis			
Cerebral haemorrh. ± oedema (61 patients)	49 %	51 %	50 %
Cerebral haemorrh. ± oedema			
Normal lungs (23 patients)	26 %	12 %	18 %

in the mature, while all other brain lesions—each only present in a few patients—were almost evenly distributed in the two groups.

Table 2 shows the combinations of causes of death. 16 per cent, or 20 patients, a majority of whom were premature, had no brain damage. Correspondingly there was a preponderance of mature infants in the 18 per cent, or 22 cases, which had only cerebral changes. However these groups are small. In the largest group (65 per cent) with both cerebral and pulmonary changes, the proportion of mature and premature patients was about equal.

Secondary findings

In one patient, who had severe intracranial haemorrhage, autopsy revealed a mild internal hydrocephalus and a unilateral double renal pelvis and ureter.

One patient as well as a tentorial tear had a thrombosis of the transverse sinus. Apart from these two cases no additional intracranial abnormalities were observed.

Moreover malformations were observed in only two patients. In one infant, who had an intracranial haemorrhage as well as cerebral oedema and atelectases, a horseshoe kidney was found. Another patient with a tentorial tear had a mild goitre and slight hyperplasia of the thyroid.

Persistent ductus arteriosus and patent foramen ovale, which can hardly be considered malformations at that age, were frequent. They were found to be co-existent in 48 per cent of the cases. Persistent ductus arteriosus was found in a total of 56 per cent and patent foramen ovale in 53 per cent of the cases, with no appreciable difference between the weight groups.

No cases of hyaline membrane disease were disclosed, however, no histological studies of the lungs had been carried out.

Abnormal intrathoracic findings were as follows. One case of haemato-pneumothorax following rupture of the inferior lobe in the left lung; one of mild hydrothorax, seven cases of tracheo-bronchitis, one case of pneumonia, one patient had subendocardial haemorrhage and four had sub-pericardial haemorrhages. Two of the latter also had petechial haemorrhages in the thymus, as had two further patients.

Abnormal intra-abdominal findings were: Two cases of intraperitoneal haemorrhage, one of unknown origin and one following rupture of the spleen, two cases of subcapsular haemorrhage of the kidney three of subcapsular haemorrhage of the liver. Fourteen patients had varying degrees of suprarenal haemorrhage, one had parenchymatous liver degeneration and uric acid infarcts in the renal papillae.

Even though some of these conditions undoubtedly represent contributory causes of death, those listed in Table 2 were considered by the pathologists to be the primary causes.

2 Survivors of the neonatal period

The 153 patients surviving the neonatal period have been divided into four groups.

1 29 patients with severe cerebral sequelae

These patients, representing 11 per cent of the total series and 19 per cent of the survivors, are again divided into three groups.

- 1) 18 patients were mentally retarded and had severe neurological symptoms,
 - 2) 7 patients were mentally retarded and had physical handicaps of varying degrees,
 - 3) 4 patients were of normal intelligence, but had definite, though not disabling neurological symptoms
- 18 patients were boys, 11 were girls.

Table 3 lists the principal clinical findings. (For details see case reports nos. 1 to 29)

Heredity Family histories failed to reveal cerebral disease except in two cases (nos. 11 and 23) where there was a history of epilepsy in close relatives. Both these patients were mentally retarded and one had seizures.

The mortality was high in this group 12 patients out of 29 had died. All of these were mentally retarded, 11 also had quadriplegia, the twelfth exhibited no neurological features, but had a severe hydrocephalus. The commonest cause of death was infection of the respiratory tract. One patient had died from meningitis. The age at death ranged from 2 months to 4½ years, seven were from 2 to 3 years old, three died before their second year and two were well over 4 years old.

The mental development was seriously retarded in the great majority of the first two groups sixteen of the children were under the care of Statens Andssvageforsorg (S A.) (the National Service for the Mentally Retarded) Of the remaining nine, four had died at the age of 2 months, 6 months, 1½ years and 2 years, respectively (Nos. 3 10 17 and 1) It can be assumed that they would have been under the care of S A had they lived.

Of the last five, three with obvious mental defects were not, however under public care primarily owing to the refusal of their parents. The remaining two probably had a subnormal intelligence, but evaluation was difficult because of multiple handicaps (nos. 4 and 7)

TABLE 3
A survey of the principal clinical findings in 29 patients with severe cerebral anomalies

	Non pat.	Macro- cephaly	Hydro- cephaly	Cerebel- lous	Aphasia	Speech defect	Hype- rcalia	Seizure	Myoclo- nicus	Dead	Under care (days)
1 Mental deficiency plus a) quadriplegia b) ataxia	16 2	10 -	11 -	13 -	9 2	3 -	3 1	9 1	6 -	11 -	9 1
2 Mental deficiency plus motor retardation, no neural symptoms	7	2	3	2	6	-	1	2	-	1	6
3 Normal intelligence plus a) subacute b) paraplegia c) hemiplegia	1 2 1	- - -	- 1 -	- 1 -	- - 1	1 - -	1 - -	1 2 -	- - -	- - -	- - -
Total	26	12	6	16	17	4	5	15	6	12	16

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TABLE 4

EEG-findings in relation to the presence or absence of seizures in 29 patients with severe cerebral sequelae

	Abnormal EEG	Normal EEG	No EEG	Total
Convulsions	11	1	4	16
No convulsions	2	7	4	13
Total	13	8	8	29

measurement of the head circumference and description of brain sections.

Electroencephalograms were obtained in 21 of the 29 cases. Of these 13 were abnormal (Table 4)

EEG-abnormalities were observed in two patients who had never had seizures. One had a severe quadriplegia, and the EEG had been recorded at the age of one year (no. 9 dying when well over 4 years of age). The other patient, aged 13 years, had stasia (no. 4). Her EEG dated back to the age of 6 years. 11 of the 16 children with seizures had EEG-abnormalities (four had had no EEGs taken). One of the children with seizures had a normal EEG (no. 14) her seizures, occurring at the age of 9-10 months, showed an atypical pattern, described as twitchings and jerks. Her EEG had been taken when she was one year old. This patient, who had a quadriplegia, had been seen for the last time at the age of four years.

An additional 7 children, whose EEGs were normal, had, at least up to the time of the follow-up, been seizurefree. Of these, two had quadriplegia (no. 7 EEG taken at 2 years, and no. 8, EEG taken at 5 months) one patient had athetosis (no. 28, EEG at 5 years) and four were physically and

TABLE 5

EEG-findings in 29 patients with severe cerebral sequelae

	Number pat.	Abnormal EEG	Normal EEG	No EEG
1 Mental retardation with				
a) quadriplegia	16	9	3	4
b) stasia	2	2	0	0
2 Mental retardation without neurological symptoms	7	1	4	2
3 Normal intelligence with				
a) athetosis	1	0	1	0
b) paraplegia	2	1	0	1
c) hemiplegia	1	0	0	1

The physical handicaps were serious in most of the mentally defective. 14 out of 16 patients with quadriplegia were severely spastic, one was moderately spastic, but also ataxic (no. 2) one had a mild quadriplegia and, in addition, a severe hemiplegia following a violent convulsion at the age of 3 years (no. 6)

None of the twelve patients who had died had been able to walk. Three mentally retarded patients exhibiting neurological symptoms were unable to walk at the time of the follow-up (aged 4-14) two walked at 4 and 6 years, and two walked at around 3 years, all with difficulty. Of the mentally defectives who failed to exhibit neurological features, four walked at 2 years, one at 3 and one at about 4 years.

Of the children with normal intelligence two walked at around the age of 2 and two at about 3 years.

Seizures occurred in more than half of the patients (16 out of 29) the greatest number among quadriplegics (13 of 16)

The commonest type of seizures were generalized clonic convulsions (13 patients) One patient had fainting spells (no. 24) two patients had spells described as infantile spasms (pat. nos. 13 and 20)

Speech. 17 patients, all among the mentally retarded, exhibited severe speech defects and are listed in Table 3 as aphasic. (Seven of these, however had died before the age of 3 without ever having been able to speak) Four had moderate speech defects—three of these were mentally retarded, the fourth (no. 28) whose intelligence was normal, had a mild athetosis and impaired hearing.

Four had normal speech, and, with the exception of one mentally defective, also normal intelligence.

On four patients, all dying within the first two years of life, there was no information about speech.

Hearing defects were found in at least five patients, who also had speech difficulties of varying degrees. One was the above mentioned athetotic child of normal intelligence. The other four were mentally retarded. In two there was a complete lack of response to noise (nos. 15 and 18) the last two had a slight hearing loss. Both had been seen by an otologist.

Vision A squint was present in about half the patients. Impaired vision was thought to be a feature in six patients who had nystagmus (all of them quadriplegics) Four of these also had a squint.

Visual acuity was not measured at the follow-up examination however there was no evidence of impaired vision apart from the six cases above.

Special examinations

In a number of patients an objective evaluation of the cerebral state was obtained by electroencephalograms (EEG) pneumoencephalograms (PEG)

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c) hemiplegia	1	0	0	1
Total	29	13	8	8

mentally retarded, two being hydrocephalic, one microcephalic. (Nos 21 EEG at one year 22 EEG at 1½ years 23 EEG at 1½ years, and 25 EEG at 4½ years)

The distribution of normal and abnormal findings within the diagnostic groups is seen in Table 5

The EEG abnormalities had no common features. Detailed descriptions are found in the case reports. In seven patients without focal neurological features there were focal EEG abnormalities, with spikes or spikes and spike-waves of diverse origins. Four had generalized abnormalities with multiple spikes and spike-waves. One patient (no 15 with severe cerebral atrophy) had an atypical record with absence of activity in the central-parietal and central tracings as well as random spikes frontally and temporally. One patient (no 13) had severe abnormalities with discharges of low frequency and high amplitude over the right hemisphere. The record had a focal character not suggestive of *hypsarhythmia*. (This child had seizures resembling infantile spasms). The second patient who had attacks described as infantile spasms (no 20) had never had an EEG taken.

Head circumference was measured in 20 patients. As will be seen from Fig. 2 the measurements were above normal in four below normal in nine, and within the normal range in seven patients. An additional two patients have in Table 3 been classified as hydrocephalic: In one case (no 10) the exact figure was not stated, however the record mentioned an abnormally fast increase in the head circumference over a certain period of time, and the diagnosis had been substantiated by PEG. The second patient (no 22) had a normal measurement, but PEG revealed a mild internal hydrocephalus.

Of 12 microcephalic patients in Table 3 only nine had been measured. However two patients brains (nos 15 and 16) were found to be abnormally small on section and one patient's (no 12) record contained repeated notes describing the child as microcephalic.

As seen from Table 3 all the microcephalic patients were in the group of mentally defective as were all but one of the hydrocephalics. This patient (no 27) had paraplegia and convulsions.

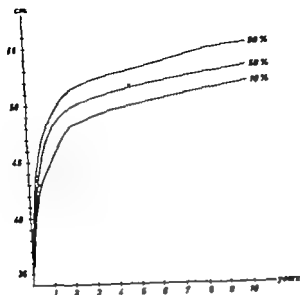
Pneumoencephalography had been performed in 13 of the 29 cases. All but one (no 28 with athetosis) were abnormal (case reports nos. 6 10 12, 13 15 16 17 18 20 21 22 and 27)

The diagnosis of hydrocephalus was confirmed in four patients and disclosed in one patient with normal head circumference. (no 22)

The cerebral atrophy that could be expected in the microcephalics was confirmed in the six cases where PEG studies had been made.

Cerebral atrophy was also demonstrated in one patient, whose head circumference had not been measured (no 6)

Boys



Girls

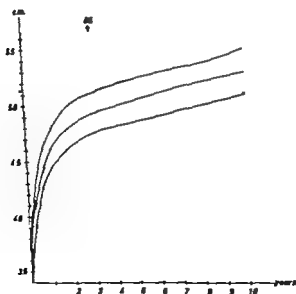


Fig. 2

Head circumference in centimetres, measured at follow-up, in 29 patients with severe cerebral sequelae. (Tracings from Vickers and Stuart, *J. Pediat.* 1943 22 155).

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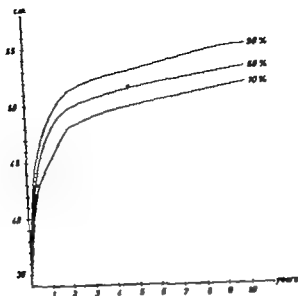
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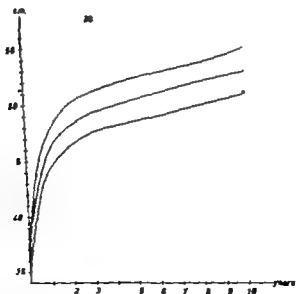


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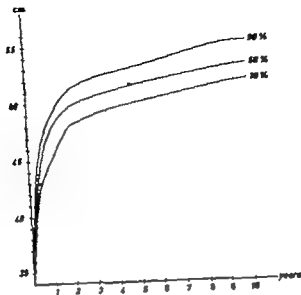
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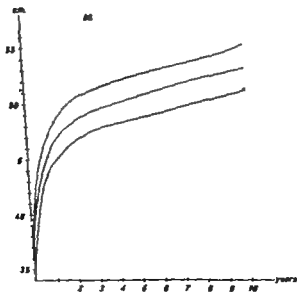


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Brain section. Detailed pathological reports were obtainable in 7 of the 12 deaths (case reports nos. 3 8 13 15 16 18 and 20)

All of these revealed severe pathological findings. Four had polyporencephaly and three had moderate hydrocephalus. One of these had dysgenesis of the corpus callosum, one had an Arnold-Chiari syndrome and in one there was a cerebral dysplasia with degeneration of the basal ganglia. No other malformations were disclosed

As seen from Table 6 cerebral atrophy has been demonstrated by PEG and/or brain section in a total of 14 cases. Six of the microcephalics and one hydrocephalic were not examined by either of these methods. However the clinical findings indicate the presence of cerebral atrophy in these cases also

This makes a total of 21 patients with cerebral atrophy out of 29 in this group

TABLE 6

Pneumoencephalography and brain section in relation to head circumference in 29 patients with severe cerebral sequelae

Head circumference	No. pat.	Abnormal PEG no brain sect.	Abnormal PEG plus brain sect.	Abnormal brain sect. no PEG	Normal PEG, no brain sect.	No PEG no brain section
Abnormally large	5	3	1	0	0	1
Abnormally small	12	2	4	0	0	6
Normal	7	1	0	1	1	4
Not measured	5	1	0	1	0	3
Total	29	7	5	2	1	14

Table 7 shows the distribution of the pathological findings within the diagnostic groups.

TABLE 7

Pneumoencephalography and brain section in 29 patients with severe cerebral sequelae

	No. pat.	Abnormal PEG, no brain sect.	Abnormal PEG plus brain sect.	Abnormal brain sect. No PEG	Normal PEG no brain sect.	No PEG no brain section
1 Mental retardation with						
a) quadriplegia	16	4	4	2	-	6
b) ataxia	2	-	-	-	-	2
2. Mental retard. No neurological symptoms	7	2	1	-	-	4
3 Normal intellig. with						
a) athetosis	1	-	-	-	1	-
b) paraplegia	2	1	-	-	-	1
c) hemiplegia	1	-	-	-	-	1
Total	29	7	5	2	1	14

TABLE 8

Relationship between EEG and PEG and/or brain section in 29 patients with severe cerebral sequelae

	Abnormal PEG and/or brain section	Normal PEG	No PEG	Total
Abnormal EEG	8	—	5	13
Normal EEG	3	1	4	8
No EEG	3	—	5	8
Total	14	1	14	29

Table 8 illustrates the correlation between EEG and PEG-findings. Three patients with confirmed brain atrophy had normal EEGs. In five cases, where no PEG was made, the clinical diagnosis of cerebral damage was substantiated by abnormal EEGs.

II Patients with minor cerebral sequelae

This group includes 24 children—9 per cent of the total material, or 16 per cent of the children who survived the neonatal period.

The group is heterogeneous, with varying degree and type of handicap, all of which, however may be traced to the perinatal period. The majority of the patients had more than one symptom of cerebral damage.

A common feature of these patients is the absence of permanent motor handicap. The mental development had been normal except in a few cases, even these, however were only mildly retarded. There were no deaths in this group.

18 patients were boys and 6 were girls. The age at follow-up was from three to five years in 8, five to seven in 7 and over seven in 9 cases.

A description of each patient is given in the case reports nos. 30-53.

The abnormal features are shown in Table 9 and each will be dealt with in detail in the following sections.

The mental development was felt to be unsatisfactory in three patients.

One of these (no. 41), on psychological testing at the age of 8, had an IQ of about 80, with allowance made for severe aphasia. Earlier testing had been abandoned due to the severe speech barrier. The second patient (no. 52) had an IQ score of 80 at the age of seven. He had begun school a few months earlier but had given up. He tried again the following year but had to be referred to a special class for backward children, where he did fairly well. No specific learning difficulties were observed.

The third patient (no. 30) had not been examined by a psychologist prior to follow-up, and testing was impractical for geographical reasons. Accord-

TABLE
A survey of abnormalities found in

Pat. no.	Mental retardation	Transient		Small size	Convulsions			Deafness
		Delayed developm.	Poor growth		Afebrile	Febrile	Branch holding	
30	(+)				+			
31					+			
32					+			
33								
34					+	+		
35		+	+					
36							+	
37			(+)					
38		+	+					
39								+
40								+
41	+	+	+					+
42		+						
43		+						
44								
45								
46								
47								
48								
49			+					
50								
51								
52	+			+				
53				+				
Total								
24	3	4	4	2	4	2	1	3

ing to her relatives she was, at the age of $6\frac{1}{2}$ somewhat backward, and she was also felt by the examiner to be rather dull.

The remaining 21 patients were in the opinion of the parents and also of the examiner of normal intelligence. Four were also seen by a psychologist.

Patient no 32 tested at the age of 12, had epileptic seizures and disturbed behaviour. He had managed fairly well in normal classes at school though he had had to remain in the second form for an extra year. He was described by the psychologist as average or bright average, showing, however evidence of organic immaturity of the receptive aphasia-type. There were no speech difficulties.

One patient (no 36) who had retarded speech and behaviour disorder scored an IQ of 112 at the age of 6.

Patient no 43 despite a pronounced lack of concentration and almost unintelligible speech, had an IQ score of 94 at the age of $2\frac{1}{2}$. In view of these handicaps his intelligence was considered to be even higher. At the age

TABLE
A survey of abnormalities found in

Pat. no.	Mental retardation	Transient		Small size	Convulsions			De
		Delayed development	Poor growth		Afebrile	Febrile	Breath holding	
30	(+)							
31					+			
32					+			
33					+			
34						+		
35		+	+		+			
36								+
37			(+)					
38		+	+					
39								+
40								+
41	+	+	+					+
42								
43		+						
44								
45								
46								
47								
48								
49			+					
50								
51								
52	+			+				
53				+				
Total								
24	3	4	4	2	4	2	1	3

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Patient no 43 despite a pronounced lack of concentration and almost unintelligible speech, had an IQ score of 94 at the age of $2\frac{1}{2}$. In view of these handicaps his intelligence was considered to be even higher. At the age

37) it was unilateral and probably caused by recurrent middle ear infection. Hence this patient has not been included in this group

In the other three (see Table 9) the hearing loss was bilateral and most pronounced for high frequencies. None of these patients had a history of otitis. All had been examined by otologists. Two had been provided with hearing-aids. All had speech difficulties in varying degree.

One patient (no. 39) had a family history of hearing loss, however the diagnosis at the National Centre for the Deaf was bilateral nerve deafness caused by premature birth. There was no family history in the remaining cases. In one (no. 40) the otologist at the Centre felt that the condition was caused by birth injury. In the second case no aetiology was suggested.

Two patients were seriously premature (BW below 1500 grams) the third was born at term.

Speech difficulties were found in varying degree in 16 patients, 12 boys and 4 girls examined at ages four to twelve years.

One patient (no. 48) who was only three years old at follow-up, has nevertheless been included, since at that time she was only able to utter a number of single words, which, though correctly pronounced, she could not combine into sentences.

The three patients with hearing loss had speech disorders in the form of imperfect formation of consonants. Two had received speech therapy at the age of six, but now spoke correctly when followed-up at the age of 12 and 11 years, respectively. The third child had "outgrown" his speech defect at the age of eight, without the aid of speech therapy.

The child who had a unilateral hearing loss (no. 37) following recurrent otitis had incorrect pronunciation until the age of six, after which his speech spontaneously became normal. The remaining children had normal hearing.

Two patients had received speech therapy at the age of seven and six respectively. They were found to have aphasia, chiefly of the expressive type. One (no. 41) was seriously handicapped. At the time of follow-up, aged 8½ years, his speech was very defective, and even as late as the age of sixteen he still had unmistakable speech trouble. The speech of the second child was characterized by defective articulation of consonants and occasional agrammatical errors. His later outcome is unknown (no. 46).

An additional patient (no. 36) had received speech therapy at the age of six because of speech defect. After a few months his speech became normal.

None of the remaining patients had received speech therapy. At follow-up, at ages 4 to 7 their speech had an immature character with occasional defective articulation of consonants. One of these children is known to have spoken normally by the age of 8½.

To sum up, considerable speech defects were found in two patients, who also had hearing loss. One patient had a severe aphasia and one had a

There were two cases of left handedness in this group

Growth Slow growth was seen in six patients. In four it was only transient, in two more prolonged.

The first four children showed poor growth during the first 6 months to two years of life. Intercurrent disease was not reported within that period, and subsequent growth was normal. Two of these children were born at term, one had a BW of 2400 grams, the fourth weighed 1440 grams only but started normal growth earlier than any of the other three.

An additional patient had a history of poor growth during the first six years of life, coinciding with numerous infectious diseases. At the time of follow-up when he was some 8 years old he had, however, reached a height 6 cm above average and weighed almost 9 kg more than the average height/weight.

Two patients, despite normal birth weights, had always been considerably smaller than average. One, at 11½ years was 20 cm below average, the other showed a deficit of 10 cm at 4½ years. None had experienced noticeable intercurrent illnesses. There were no instances of subnormal height in the families.

The remainder of this group had normal growth rates and their heights at the time of follow-up were largely within the normal range.

Convulsions were reported in six patients, all had experienced more than one episode.

In three patients there were recurrent afebrile convulsions and their EEGs showed dysrhythmia indicative of epilepsy. In one of these (no 31) the fits had ceased spontaneously at the age of three years. She had been seen last when she was six. The other two still had seizures at the age of six and twelve despite anti-convulsant therapy (nos 30 and 32).

Two of the children had convulsions in connection with fever. Patient no 33 had suffered numerous attacks of increasing duration. Patient no 34 had only one fit in connection with fever, however he also had very frequent episodes of ill-defined absence-like type. Both had normal EEGs. None had received anti-convulsant drugs. They were four and three years old at the time of follow-up.

The sixth patient (no 35) had experienced two seizures at the age of two to four years, probably precipitated by temper tantrums. He, too, had a normal EEG and had not received anti-convulsant therapy. He had been seizure-free for well over three years at the time of follow-up.

There was no family history of convulsion in any of the cases.

Two patients (nos. 30 and 32) thus had obvious epilepsy, two (nos. 33 and 34) were highly suspicious of epilepsy and two (nos. 31 and 35) had a tendency towards seizures, from which they had apparently recovered.

Reduced hearing was found in a total of four patients. In one case (no

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Two patients had received speech therapy at the age of seven and six respectively. They were found to have aphasia, chiefly of the expressive type. One (no. 41) was seriously handicapped. At the time of follow-up, aged $8\frac{1}{2}$ years, his speech was very defective, and even as late as the age of sixteen he still had unmistakable speech trouble. The speech of the second child was characterized by defective articulation of consonants and occasional agrammatical errors. His later outcome is unknown (no. 46).

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To sum up, considerable speech defects were found in two patients, who also had hearing loss. One patient had a severe aphasia and one had a

presumably mild aphasia. The remaining twelve exhibited varying degrees of retarded speech development.

The behavioural pattern of 20 children appeared to be normal however two of these were described as being unusually hyperactive (patient no. 30 with epilepsy and no 46 with a mild aphasia) one as rather reserved and touchy (no 38 with hearing loss and speech defect) and one as vulnerable and quick tempered (no 41 with severe aphasia)

Four presented obvious behavioural deviations such as hyperactivity lack of concentration and aggression (nos. 32, 36 37 and 43) All of these had additional handicaps, and precipitating environmental factors have not been definitely excluded. Three were examined by a psychologist (see p. 38)

Transient hyperactivity in the form of screaming, restlessness and reduced need for sleep that could not be attributed to external factors, were present in two children (nos. 42 and 50) during the first one or two years of life. Of these one was also over sensitive to noise. Neither subsequently had presented any behavioural problems.

Eye defects Squint was present in seven patients (see Table 9) One also had diminished visual acuity in both eyes (no 35) another in one eye (no 37) The other patients vision was normal. Only one had a family history of squint (no 49) one child (no 32) had a unilateral presumably familial cataract.

Retrolental fibrosis was not observed.

Enuresis Eight patients had been, or were still, suffering from enuresis. In only one case (no 51) was there a family history of enuresis.

Behavioural defects in varying degree were present in four (nos. 30 32, 36 and 41) All eight children had various additional handicaps.

Electroencephalography had been performed in 12 cases (see Table 9) The records were abnormal in four patients, three of whom had a history of seizures. The fourth, at the age of 12 had never had seizures (no. 36) For full details reference may be made to the case histories

In the three patients who had experienced seizures the EEG showed abnormalities of varying severity with spikes of differing location indicative of epilepsy The record of the fourth patient, who presented a behavioural defect, revealed generalized dysrhythmia.

The eight normal EEGs were recorded as follows. two patients with febrile convulsions one with breathholding spells one with aberrant behaviour and speech disorder two with reduced hearing and speech defect, and two with speech disorders, one of these being aphasic.

III Patients with mild deviations of presumably cerebral origin

In this group are included 30 patients, or 11 per cent of the total material (19 per cent of the survivors)

Like Group II it is quite heterogeneous. Some symptoms are present in each group. The reason for nevertheless including the patients in this "milder" group is the fact that their symptoms were less pronounced and, in contrast to Group II usually occurred singly

In addition some of the patients had presented symptoms only transiently and were found to be normal at the time of follow-up.

Motor handicaps had not been demonstrated, and the mental deviations had been of a less definite kind than in the previous group

Eighteen children were boys, twelve were girls. 12 children were aged three to five, 9 were five to seven, and 9 were more than seven years old.

The symptoms are listed in Table 10. For a description of individual cases reference should be made to case reports nos. 54 to 83

The following sections contain an analysis of each symptom.

The mental development of these children was felt by the examiner as well as by the parents to be within normal limits in all cases. However, the evaluation is not entirely comprehensive, as no psychological tests had been performed and, in addition, many of the children were very young at the time of follow-up. Of the nine children attending school five had reading difficulties and achieved only medium marks at school, and one had had to remain a second year in the first form. These children's intelligence was felt to be within the normal range (cf. p. 46).

Motor development had been temporarily retarded in ten patients, six of whom also transiently showed poor growth. Until normal development started, lethargy had been marked, half the children were said to have been very flaccid.

The majority of the patients were able to sit up at the age of 9 to 10 months, although one not until the age of 18 months. Four walked at 14 to 15 months and the remainder at 18 months to 2 years. Of the first four one was premature, having a BW of 2400 grams, the remainder were full-term. Of the remaining six 4 were premature, with a BW of 1800-2000 grams. Their motor pattern had not been unusual except in the case of two patients. One (no. 64) was suspected of having cerebral palsy when admitted to hospital at the age of 4 months because of increased muscle tone and exaggerated tendon reflexes. She had evident rickets at that time. Follow-up examination revealed no spasticity. The second patient (no. 60) aged 10 years at follow-up, had always been slow at walking and running, characterized by rather pronounced flat feet. Although this had not altered over

TABLE
A survey of the findings in 30 patients

No. pat.	Transitory retarded development	Transitory poor growth	Small height	Convulsions	
				Febrile	Brain holding
54					
55				+	
56				+	
57	+	+	+	+	+
58	+				
59	+	+			
60	+				
61	+				
62	+	+			
63	+				
64	+	+			
65	+	+			
66	+	+			
67					
68					
69					
70					
71					
72					
73					
74					
75					
76					
77					
78					
79					
80					
81					
82					
83					
<hr/>					
Total					
30	10	6	2	3	1

the years, his motor pattern was otherwise normal. Hand movements were normal, and neurological examination was negative.

The remaining patients had developed normally sitting up at about 6 months and walking at about one year.

There was one case of left-handedness (familial).

Growth. Transient retardation of growth was reported in six patients (cf Table 10). In three it persisted until the third to eighth month, and in the other three for the first two years of life. Growth later became normal except in one case where the height at the age of 7½ years was found to be

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A survey of the findings in 30 patients

No. pat.	Transitory retarded development	Transitory poor growth	Small height	Convulsions	
				Febriile	Brach holding
54					
55				+	
56				+	
57	+		+		+
58	+	+	+	+	
59	+	+			
60	+				
61	+				
62	+	+			
63	+				
64	+	+			
65	+	+			
66	+	+			
67					
68					
69					
70					
71					
72					
73					
74					
75					
76					
77					
78					
79					
80					
81					
82					
83					
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Total					
30	10	6	2	3	1

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school. In one case (no. 75) there was also left-handedness, which—like the dyslexia—was familial. One additional patient only (no. 80) had a family history of dyslexia.

Of the remaining children in this group 21 had not reached school age; three had just begun school, so that no evaluation was possible at the time. The last patient in the group, who was 13 years old, had no reading difficulties.

Speech development had been normal in all the children. One had a stammer however at the time of follow-up, at the age of $7\frac{1}{2}$ years, it was negligible. He had been receiving speech therapy for several years.

No hearing defects were observed.

Eye symptoms: Squint was present in eight patients, five of whom had a family history of this defect. Two (nos. 72 and 82) had diminished visual acuity in one eye. The vision of the remaining children was considered normal, and no other eye abnormalities were noted.

Enuresis was present in six patients, aged $4\frac{1}{2}$ to 10 years. One patient only (no. 77) had a family history of enuresis.

None of the six children had behaviour disorders: two (nos. 76 and 77) were described as very sensitive. One further patient had dyslexia and a squint, and one had a (familial) squint.

Additional abnormalities: One patient (no. 57) had stethoscopic evidence of heart disease giving rise to no symptoms other than, possibly small height, which however was familial.

One patient (no. 64) at the age of $3\frac{1}{2}$ years had a very small head circumference (48 cm). Her development had been retarded during the first two years of life, but was subsequently normal. Head circumference of the other patients was normal.

Patient no. 81 had a left-sided palsy as the only neurological feature present at follow-up. She had been delivered by forceps.

Electroencephalograms were normal in all six cases in which EEG-studies had been performed.

IV Patients with no abnormal features

70 children—40 boys and 30 girls—showed no abnormal features, i.e. 25 per cent of the total material and 46 per cent of the survivors. At follow-up 28 were aged three to five years, 23 were five to seven years, and 19 were more than seven years old.

Their mental development was estimated as normal on the basis of clinical observation and history. Those children who had already reached school age had started at the normal time and had done well. None had revealed difficulties of learning.

BW being 1800 grams. (This patient exhibited poor growth during the first four months only)

At the time of follow-up all except two had reached normal height: the one mentioned above, and patient no. 56, whose height at $4\frac{1}{2}$ years was 111 cm below average. There was no history of periods with specifically poor growth or intercurrent disease. She was a twin, her BW being 1800 grams (the co-twin died when two days old). There was no family history of small size.

Convulsions occurred in four patients: three had a single episode only of generalized clonic convulsions in connection with hyperpyrexia at the age of 4, 2 and 1 year respectively. The observation period following these episodes was 1, 2 and 6 years, respectively, and was thus too short for a prognostic evaluation in the first two cases.

The fourth patient had suffered repeated episodes of convulsions until 18 months of age, precipitated by crying. At the time of follow-up, three years later, there had been no further seizures.

None of the four patients had a family history of convulsions.

Behaviour disorders Six patients had exhibited transient hyperactivity in the form of crying, motor restlessness, occurring also when asleep, and often associated with a diminished need for sleep. No environmental cause was apparent, and the symptoms subsided during the second year of life. These children presented no behaviour problems later on.

Five patients aged 4 to 10 years were reported to have behaviour disorders in the form of hyperactivity and violent temper. The mothers denied precipitating environmental factors. One of these children had had febrile convulsions, another was dyslectic and had temporarily shown retarded motor development. One had a (familial) squint and a marked sensitivity to noise. The fourth also had a (familial) squint. The fifth was otherwise normal.

Two patients (nos. 76 and 77) showed no obvious behavioural deviations, but were reported to be of "nervous temperament" and easily frightened. One was a stammerer. Environmental causative factors were also denied in these cases.

An additional patient (no. 66) appeared rather restless; however, the parents ascribed this to "sibling jealousy". None of the remainder had presented behaviour disorders.

Dyslexia was present in five patients, all boys, aged 9 to 12 years at the time of follow-up.

One of these children had been referred to the Institute for Dyslectics at the age of 12 following several years' reading difficulties; one had had to repeat the first form; two had had to attend special classes in normal schools; one had attended normal schools through his education. All were felt to have normal intelligence, though they obtained only medium marks at

school. In one case (no. 75) there was also left-handedness, which—like the dyslexia—was familial. One additional patient only (no. 80) had a family history of dyslexia.

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70 children—40 boys and 30 girls—showed no abnormal features, i.e. 25 per cent of the total material and 46 per cent of the survivors. At follow-up 28 were aged three to five years, 23 were five to seven years, and 19 were more than seven years old.

Their mental development was estimated as normal on the basis of clinical observation and history. Those children who had already reached school age had started at the normal time and had done well. None had revealed difficulties of learning.

BW being 1800 grams. (This patient exhibited poor growth during the first four months only)

At the time of follow-up all except two had reached normal height: the one mentioned above, and patient no 56 whose height at $4\frac{1}{2}$ years was 8 cm below average. There was no history of periods with specifically poor growth or intercurrent disease. She was a twin, her BW being 1800 grams (the co-twin died when two days old) There was no family history of small size.

Convulsions occurred in four patients three had a single episode only of generalized clonic convulsions in connection with hyperpyrexia at the age of 4 2 and 1 year respectively The observation period following these episodes, was 1 2 and 6 years respectively and was thus too short for a prognostic evaluation in the first two cases

The fourth patient had suffered repeated episodes of convulsions until 18 months of age, precipitated by crying. At the time of follow up three years later there had been no further seizures.

None of the four patients had a family history of convulsions.

Behaviour disorders Six patients had exhibited transient hyperactivity in the form of crying, motor restlessness, occurring also when asleep, and often associated with a diminished need for sleep. No environmental cause was apparent, and the symptoms subsided during the second year of life. These children presented no behaviour problems later on.

Five patients aged 4 to 10 years were reported to have behaviour disorders in the form of hyperactivity and violent temper The mothers denied precipitating environmental factors. One of these children had had febrile convulsions, another was dyslectic and had temporarily shown retarded motor development. One had a (familial) squint and a marked sensitivity to noise. The fourth also had a (familial) squint. The fifth was otherwise normal

Two patients (nos 76 and 77) showed no obvious behavioural deviations, but were reported to be of "nervous temperament" and easily frightened. One was a stammerer Environmental causative factors were also denied in these cases

An additional patient (no 66) appeared rather restless however the parents ascribed this to "sibling jealousy" None of the remainder had presented behaviour disorders.

Dyslexia was present in five patients, all boys, aged 9 to 12 years at the time of follow-up

One of these children had been referred to the Institute for Dyslectics at the age of 12 following several years reading difficulties one had had to repeat the first form two had had to attend special classes in normal schools one had attended normal schools through his education All were felt to have normal intelligence, though they obtained only medium marks at

of mixed type. *Barclay* (1956) found as many as 70 per cent out of 144 children with c. p. *Skarvedt* (1958) reported a percentage of 47 in a series of 370 patients with c. p. Finally *Eastman et al.* (1962) demonstrated neonatal abnormalities in 24 per cent of 689 cases of c. p. compared with only one per cent in a comparable series of controls. *Roboz* (1962) found neonatal disease, including primary asphyxia, in 40 per cent of 198 children with c. p.

In the present material the incidence of c. p. is very high. 14 per cent compared with about 1.5/1000 in a normal population.

2. Mental deficiency

Similar studies, though less extensive, have been made on severe mental deficiency. *Larsen* (1931) in a series of 223 patients with mental retardation of exogenic origin, concluded that birth trauma was the most probable causative factor in 22 per cent of the cases.

Pasnowecki and Lillienfeld (1955) found, in a survey of mentally retarded children, that 18 per cent had exhibited complications in the neonatal period compared with 7.5 per cent in a control material.

At postmortem examination *Benda* (1956) demonstrated abnormal findings of perinatal origin in 24 per cent of 258 mentally defective patients.

Drillien Jameson and Wilkinson (1966) analysed a large series of mentally defectives (IQ below 70) for a variety of factors, including aetiology. In 13 per cent of 211 patients with an IQ below 55 and in 11 per cent with scores between 55 and 69 perinatal disorders were considered the most important aetiological factor. All these children had displayed varying symptoms during the neonatal period.

3. Seizures

The overall percentage of seizures in the present series is 18. If single episodes are disregarded, the percentage is 14. —Among the 29 patients with persisting neurological features the incidence, as already mentioned, was over 50 per cent and highest in quadriplegics (13 out of 16). Among the 124 patients with no neuro-muscular manifestations the incidence was 9 per cent; after omitting single episodes, 5 per cent. These figures include the febrile convulsions occurring in 4 per cent of the 124 cases.

The incidence of seizures in childhood is difficult to establish with certainty as not all children who have seizures are admitted to hospital and registration thus is incomplete. *Thom* (1941–42) gave a figure of 7 per cent among 3461 children under the care of the Community Health Association in Boston. *Bridge* (1949) found the same percentage among children admitted to Johns Hopkins Hospital over a three-year period. *Pache* (1954)

Their growth had been normal, and their height and weight as well as head circumference were within normal limits

Motor development had been normal in all cases, though 10 had not sat up until the age of 9-10 months and had not walked until the age of 12-18 months. At no time had there been a history of flaccidity or apathy

There were five cases of left handedness, of which two were familial. Convulsions did not occur

All children had acquired toilet habits at the usual time.

There were no appreciable behaviour difficulties.

An EEG which was normal, had been recorded in only one patient, owing to "nightmare like" nocturnal spells.

Discussion

All the features described above are presumably of cerebral origin. Whether or not they are sequelae of the neonatal condition will be discussed in detail in the following section.

1 Cerebral palsy

So far as Group I (severe handicaps) is concerned the relationship can hardly be questioned. Ever since Little's days there has been widespread agreement that patients suffering from cerebral palsy (c. p.)—whatever the origin—have frequently had neonatal disorders. Among recent studies (all retrospective) that of *Asher and Schonell* (1950) reported 221 cases of congenital c. p. in full-term children 38 per cent of whom had exhibited various symptoms during the neonatal period. *Belnap et al.* (1950) found that about half their series of 419 patients with c. p. had suffered birth injury and a large majority of these had exhibited neonatal symptoms. *Lilienfeld and Parkhurst* (1951) found in 561 children with c. p. a significantly higher incidence of complications during pregnancy delivery and neonatal period than in a comparable control series. They felt that there existed "a continuum of reproductive casualties" extending from foetal death to decreasing degrees of brain damage manifesting in neuropsychiatric disturbances. *Eastman and De Leon* (1955) reported "poor neonatal condition" in 42 per cent of 96 patients with c. p. *Plum* in a study of c. p. (1956) reported the presence of neonatal symptoms in 22 per cent of 87 hemiplegics, in 41 per cent of 91 paraplegics, in 66 per cent of 202 quadriplegics, and in about 60 per cent of 92 athetotics. *Crothers and Paine* (1959) made similar observations. neonatal symptoms were recorded in 28 per cent of 124 hemiplegics, in 36 per cent of 86 quadriplegics, in 47 per cent of 61 patients with extrapyramidal conditions and in 33 per cent of 57 patients with c. p.

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found as few as 3.7 per cent among the children admitted to the University Clinic of Paediatrics at Munich over a nine year period.

The incidence of febrile convulsions reported below is subject to the same reservations governing seizures in general. However as in the latter case, they are fairly consistent. *Bridge* (1949) attributed 2 per cent of the admissions to Johns Hopkins Hospital over a three-year period to "febrile convulsions". *Bamberger and Matthes* (1959) in another hospital series, found 1.9 per cent. Among all children born in Heidelberg over a period of several years the percentage was 0.5-1.5 up to the fourth year of life. *Friderichsen and Melchior* (1954) in a hospital series over a four year period reported a percentage of 4.5.

It is well known that seizures are a common feature in children with cerebral damage. The incidence of seizures in children with c. p. has been assessed in several studies. Thus *Perlstein* (1952) found this symptom in 40 per cent, occurring more often in spasms (50 per cent) than in athetotics (15 per cent). *Plum* (1956) found a frequency of 46 per cent in quadriplegics, 43 per cent in ataxics, 21-24 per cent in athetotics and 13 per cent in paraplegics.

The rates found in the present material are very similar although slightly higher than those given in non-selected series.

The aetiology of seizures is often obscure, though several workers have demonstrated a relation to birth injury.

Livingston (1954) in a survey of 4158 epileptic children, found a history of head injury in 46 per cent. However in only 36 per cent was it felt to be severe enough to be considered the causative factor. In 15 per cent of his large material the aetiology was thought to be birth injury. In *Livingston's* opinion it is not possible, due to the difficulty of the neonatal diagnosis, to predict the frequency of later epilepsy in infants suffering birth injury.

Peterman (1946) found a history of birth trauma in 14.2 per cent of a large series of epileptic children.

Bridge (1949) thought that natal or neonatal damage was an aetiological factor in 23 per cent of 742 epileptic children.

Nielsen and Courville (1951) felt that birth injury would seldom be the only causative factor in epilepsy except where there was a hereditary predisposition.

In a series of 535 epileptics, children as well as adults, gathered together by *Smith, Robinson and Lennox* (1954) birth injury was found in 30 per cent and a prenatal aetiology was traced in 13 per cent of the cases.

Pasamanick and Lillenfeld (1955) studied the birth histories of 564 epileptic children and found the incidence of abnormalities during pregnancy, delivery and the neonatal period to be significantly higher than in a comparable control material. The figures were identical whether the children had

a family history of epilepsy or not. However they found a significantly higher number of abnormalities in children whose seizures began within the first year of life.

In a series of 270 epileptic children *Bamberger and Matthes* (1959) found very high rates. They concluded that in 30 per cent the seizures could be ascribed to birth injury in 16 per cent to prenatal malformations, and in 8 per cent to either one or the other. *Peiffer's* figures (1962-63) were considerably lower he ascribed 8.7 per cent to birth injury and 7.7 per cent to focal abnormalities, as demonstrated by pathological studies in 298 epileptic patients.

Among workers considering birth injury to be a possible aetiological factor in febrile convulsions *Petersen* (1952) found an incidence of 11 per cent in a series of 302 patients. *Bamberger and Matthes* (1959) found a rate of 6.8 per cent birth injuries in 634 patients, and stated the frequency of birth trauma in just over 2000 births at the same time to be lower than 2 per cent. *Horstmann and Schwenning* (1963) disclosed a history of head injury in 17 per cent of 108 children with febrile convulsions, among which birth injury was by far the commonest.

It is evident that the connection between neonatal disorders and seizures cannot be proved. However, it may be said to exist with reasonable certainty.

4 Behaviour disorders

It is an extremely difficult task to establish the reasons for deviation from what is recognized as normal behaviour. However a definite behavioural pattern seems strikingly common in children who have sustained brain damage in early life—even in the absence of neurological manifestations. This pattern is characterized by pronounced lack of concentration, hyperactivity, aggression, emotional instability and immaturity. It has been described with increasing frequency during the last 20 years (see among others *Bender* 1945 *Precision* 1945 *Rosenfeld and Bradley* 1948, *Bakwin* 1949 *Rogers and Libensfeld* 1955 *Ingram* 1956, *Lauffer and Denhoff* 1957 *Silver* 1958, *Lempp* 1964 and, for an extensive review of the literature *H. H. Nielsen* 1966).

The incidence of behaviour disorders (b. d.) due to brain damage is difficult to establish. It varies considerably in reports from clinics concerned with the care of these children. The diagnosis has been made more frequently in recent years, as interest has increased and the diagnosis has been facilitated by the demonstration of the frequent co-existence of perceptual disorders.

EEO has been used in the diagnosis. *Jasper et al.* (1938) in 71 patients with b. d. found abnormal records in about three-quarters of the children with

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neonatorum, neonatal anoxia and birth trauma, hereditary disorders and sequelae of maternal rubella) They found similarities in the audiograms of children with hearing loss due to morbus haemolyticus neonatorum and to anoxia, both groups showing a preponderance of selective hearing loss for high frequencies. This finding was substantiated by Fisch (1955), who found these similarities in the audiograms, though not consistent, but with suggestive frequency Johnson (1954) found, in 111 children with perceptual deafness, that in 10 per cent of the cases where no hereditary factors were demonstrable, the aetiology was perinatal asphyxia in another 10 per cent it was premature birth, without asphyxia. In these groups he found a well-defined hearing loss for high frequencies. His findings were supported by Maran (1966). Flottorp-Morley and Skarvø (1957) carried out audiological examinations in 10 athetotics (children and adolescents) which revealed a specific hearing loss for high frequencies. This was ascribed, however to cochlear defects.

Astrup (1959) examined ten pairs of twins, of whom one twin had a typical selective hearing loss for high frequencies, while the co-twin had normal hearing. Six of the ten pairs were premature. He found that loss of hearing was more likely to occur in a premature twin, if the BW was considerably lower than that of the co-twin, or if birth complications which predisposed to anoxia, such as breech presentation, were present, particularly in a first-born twin. However perinatal anoxia also led to partial hearing loss in full-term infants.

McDonald (1964) demonstrated moderate to severe hearing loss in 1.8 per cent of 1081 children with a BW below 1800 grams, when followed-up at the age of 6 to 8 years. The rate increased with decreasing gestational age (4 per cent in children born before the 33rd week and 0.6 per cent in children born after the 33rd week). Moreover the incidence was significantly higher (10.7 per cent) in children who had exhibited cyanotic attacks during the neonatal period than in those who had not (3 per cent) (In both groups the gestational age was below 33 weeks). He concluded that anoxia during the early postnatal period could result in impaired hearing in the very premature. This contrasts with the observations of Davey (1962) made on a much smaller series of premature children examined at a comparable age. A considerable number of these children had hearing defects, but on the whole, practically all the cases could be attributed to extracerebral causes and were unrelated to neonatal anoxia or convulsions. Davey considered that the role of prematurity had been overestimated and he regarded the basic pathological condition as needing clarification.

In the present material two of the hard of hearing patients who were neurologically normal had a BW below 1500 grams the third child was born at term.

a history of cerebral damage and in somewhat less than half of those who had not. Likewise, *Gottlieb* (1945) found EEG-abnormalities in about half his 67 children with b d. In the absence of organic cerebral damage. *Kennard* (1947) reported 65 per cent of abnormal EEG-records among a large series of children with b d. against 16 per cent in a comparable control material. *Schlange* (1963) demonstrated a positive correlation between EEG-changes and specific b d a history of early brain damage and neurological abnormalities.

In the present material EEG-records were abnormal in two of the nine children who had b il (one also had seizures). In four EEG-records were normal and in three EEG had not been carried out.

5 Hearing defects

Impaired hearing was demonstrated in a total of eight patients, five of whom were among the severely handicapped in Group I (nos. 4 15 18 22, 28). The type of hearing loss could not be specified in these cases. Three patients with no persisting neurological features (nos. 38 39 and 40) had hearing loss for high frequencies only. The literature contains several studies, pathological as well as clinical on hearing loss of this type.

Lewy and Kobrak (1936) demonstrated major structural differences between the dorsal and central cochlear nuclei and found the dorsal nucleus to be the only portion of the auditory pathways with a distinct separation of the fibres conducting high and low frequencies. The former are concentrated in the dorsal nucleus, which was considered to be particularly vulnerable being the phylogenetically younger portion of the cochlear nucleus, more vascular and less protected (*Craigle* 1938 and *H S Dunning and Wolf* 1937). Furthermore its structure is very complex.

Hall (1963) performed pathological studies on the auditory pathways in 50 newborn infants dying after pronounced asphyxia, as well as in 10 non-asphyxiated controls and in experimental animals (kittens). He found that no other part of the auditory pathways was as sensitive to hypoxia and exhibited such marked alterations as the cochlear nucleus.

In comparable studies *Hall* (1965) found cell destruction to be greater in the dorsal than in the ventral portion of the cochlear nucleus.

In contrast, *Buch* (1966) inferred from histological examination of the inner ear of the newborn that lesions following birth injury would especially affect the labyrinth. His series comprised 73 infants dying during the neonatal period (the majority being premature) and he found labyrinthine haemorrhages in 32. He thought that breech presentation, transverse presentation and forceps delivery were predisposing factors.

Fisch and Osborn (1954) performed audiometry on a large number of children with congenital hearing loss of various origin (morbus haemolyticus

had evidence of brain lesions, mainly following birth injury or severe asphyxia. He had no control series.

Kort and Pasamanick (1959) who introduced the concept of "a continuum of reproductive casualties" felt that reading disorders were part of this continuum. They found, among dyslexics, a significantly higher incidence of pregnancy complications than in a control series, and moreover a higher though not statistically significant, incidence of neonatal abnormalities such as asphyxia, cyanosis and convulsion. Relatively more children with severe reading difficulties were found in the group with perinatal complications.

Prechtl (in *Money Reading Disability* 1962, p. 187) in a material of 50 children with behaviour disturbances and difficulties at school, found reading disorders in 45 (none of whom had exhibited neurological or psychiatric symptoms). All the patients also had choreatic twitching of face, tongue, neck and body and nearly all also had twitching of the eye muscles. In addition, more than half showed ambilaterality. In 50 per cent of the cases there had been complications during pregnancy and in 46 per cent neonatal disorders were reported. *Prechtl* suggested that some children would have reading difficulties because of inability to focus for long enough time associated with a short concentration span due to the choreatic activity. These functional deficiencies might further delay the development of cerebral dominance and of a function as complex as reading. He thought that minimal brain damage was a possible aetiology.

Zangwill (1960) found a history of cerebral damage or "minor epilepsy" to be fairly frequent in dyslexics. He suggested that individuals who were ambilateral or had a family history of ambilaterality might be especially prone to minimal brain lesions including birth injury and particularly likely to develop subsequent language disturbances (p. 25).

Critchley (1964 p. 17) cautioned against ascribing dyslexia to a focal brain lesion, because one would then have to ignore the important role played by immaturity in proportion to chronological age and cortical development. In any event delayed reading due to birth injury would, according to *Critchley* be entirely different from a specific dyslexia.

Ford (1960 p. 258) pointed out that no postmortem studies have been published and that it is unknown whether a developmental defect of the cerebral cortex is present or not.

In spite of the fact that most authorities have ascribed dyslexia to dysfunction or immaturity of the brain, the fundamental aetiology remains obscure, and the possibility of perinatal complications as precipitating or causal factors has not been excluded. With this question still unresolved, the dyslexics in this material have been grouped together with the children exhibiting sequelae.

6 Dyslexia

Congenital dyslexia in many respects resembles the later acquired disorder alexia. This fact has been an incentive in the search for a traumatic aetiology of the congenital disorder as well. However dyslexia is probably not a sharply defined clinical and aetiological entity but a more heterogenous condition. Even its demarcation has met with considerable difficulties, since a number of other reading defects must be excluded, viz those secondary to general mental retardation, visual or auditory defects, word deafness, speech disorders and emotional disturbances (cf *Hermann 1955 English edition 1959*) In view of the obvious familial factor and the co-existence of disturbances of language and lateralization, *Orton (1925 general review 1937)* ascribed dyslexia to defective or delayed development of unilateral cerebral dominance, and this theory has been supported by many writers (*Creak 1936 and Gallagher 1950* among others) Most writers dealing with this condition emphasise the hereditary factor and consider dyslexia to be the result of cerebral dysfunction or delayed development, stressing to a lesser or greater degree the importance of disturbances of lateralization (see *Skydsgaard 1942, Hallgren 1950 Hermann 1955 1959 Drew 1956, Eidinger 1962 and Reinhold 1963* among others)

Other workers do not exclude an organic factor *Hinshelwood (1917)* thought that cerebral damage of varying degree or cerebral dysfunction might give rise to varying degrees of dyslexia.

Eustis (1947) found the above mentioned symptoms in connection with a family history of clumsiness, and suggested that the cause of all the symptoms was delayed neuromuscular maturation due to slow myelinization.

Gesell and Amatruda (1947 p. 246) suggested that dyslexia could be a developmental manifestation of minimal cerebral damage, since developmental retardation might precede recovery from the injury They drew a parallel between behaviour disorders, speech difficulties and poorly developed unilateral dominance. A high correlation with minimal birth injury probably higher than generally recognized, was demonstrated.

Rabinovitch Drew De Jong Ingram and Whitey (1954) also suggested that dyslexia was part of a more generalized disturbance of integration, presumably a developmental dysfunction. They did not, however exclude the possibility of unrecognized minimal birth injury as an aetiological factor

Malmquist (1958) failed to find an increased incidence of birth trauma or natal abnormalities however his material showed a definite relationship with premature birth. In his opinion dyslexia was a variation within the normal range. In a very large group of children with reading difficulties analysed by *Eames (1959)* 14 per cent were found to present evidence of cerebral damage against 11 per cent in a control series of comparable size *Nicholls (1960 and 1965)* found that 2 per cent of children with dyslexia

Sillerman, Gibbs and Perlstein (1952) studied EEG-changes in children with squint. They demonstrated the presence of focal EEG-abnormalities in the occipital region in 74 per cent of children with cerebral palsy who had a squint and only in 38 per cent in c. p. children who had none. Similar EEG-changes were present in 20 per cent of a group of normal children with squint and in only 0.5 per cent in a group of controls. *Trojaborg* (1966, p. 41) could not reproduce this difference. He found occipital EEG-changes in some 15 per cent of c. p. children, whether squint was present or not.

EEGs had been carried out in 21 of the children with squint in the present material. 13 were normal and 8 abnormal however only one of these (no. 30) had changes in the occipital region.

2. Electroencephalography

The number of available EEG-studies is too small to allow an estimation of the incidence of EEG-abnormalities. Of 40 recordings 17 were abnormal (13 in Group I, 4 in Group II, none in Groups III and IV) and 23 were normal (8 in Group I, a total of 15 in Groups II, III and IV).

The same reservation applies to the following studies. At a follow-up of 201 children with evidence of neonatal intracranial damage, or asphyxia, *Merrill and Korda* (1953) carried out EEG studies on 54 patients and found abnormalities in 37. Among these one patient had developed normally the remainder had epilepsy mental retardation or cerebral palsy. *D'Avignon and Kellson* (1953) carried out an EEG-follow-up in 44 out of 61 children with a history of neonatal asphyxia. One third, all exhibiting cerebral symptoms, had severely abnormal tracings. The records of a further third showed minor dysrhythmia, and a third were normal. The children in the last two groups were clinically normal. The authors emphasised that the slight dysrhythmia might be due to cerebral damage to a certain degree, but that EEG-abnormalities could also be seen in normal subjects. The frequency of mild dysrhythmia in normal children is estimated as follows. *Perlstein, Gibbs and Gibbs* (1947) 16 per cent; *Polacek et al.* (1965) 11.6 per cent; *Brandt, Brandt and Vollmond* (1961) 6 per cent (of 120 normal children below the age of 15).

7 Squint

Squint was found in 30 patients or 20 per cent of all survivors of the neonatal period. This is in line with *Rydberg's* finding (1932) in a series of children presenting severe cerebral symptoms during the neonatal period (25 per cent).

The incidence of squint in a normal population is estimated to be about one or two per cent, somewhat higher in childhood. *Thomsen* (1924) found 3 per cent in children aged 5 to 6 16 per cent in the age group 12 to 13 *McNeil* (1955) reported 2.7 per cent (age 5 to 15) *Frandsen* (1960) and *Millar* (1965) both found 4.5 per cent.

In the present material about half the patients with a squint were found in the group of 29 patients with severe cerebral sequelae (incidence 51 per cent). It is well known that squint is commonplace in children with cerebral palsy *Guibor* (1953) observed a squint in 60 per cent of his material of children with cerebral palsy *Plum* (1956) in a series of 543 children with cerebral palsy found an incidence ranging from 23 to 72 per cent, lowest in spastic hemiplegics, highest in patients with athetosis due to neonatal jaundice. In patients with quadriplegia and ataxia the rate was about 50 per cent. *Douglas* (1961) in a comparable material of 168 patients, observed a frequency of 45 to 47 per cent, rising from 33 to 58 with increasing severity of handicaps including mental deficiency.

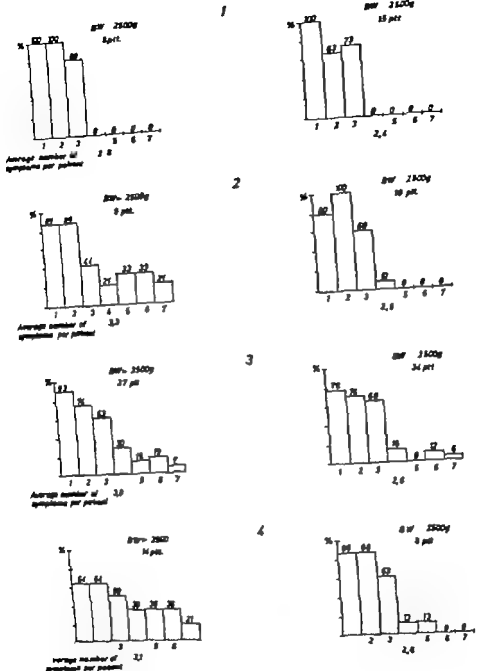
Moreover it has been demonstrated that squint is more frequent in mentally defectives than in children of normal intelligence. Thus *Frandsen* (1960) found a squint to be present in 12.4 to 24.3 per cent of children attending schools for mentally defectives, and in 33 per cent of children in an institution for mentally defectives.

In the Groups II-IV of the present series (124 patients with minor or no handicap) 15 children had a squint (12 per cent) i.e. a higher incidence than in a group of normal children and lower than in a group with severe cerebral defect. Even excluding the six children who had a family history of squint the frequency is still at the upper normal limit (7 per cent).

Squint is not an aetiological entity and it is not always possible to establish its origin. A survey of aetiological possibilities has been made by *Frandsen* (1960) among others.

The higher incidence of squint in children with diverse cerebral defects supports the likelihood of a common aetiology in these patients. It may be added that higher incidence of squint has also been demonstrated in children with symptomatic epilepsy viz. 13 per cent in children of normal intelligence, 28 per cent in mentally defectives and 37 per cent in children with a history of birth injury (*Millar* 1965).

Monosymptomatic squint in this material was found only in two patients (in Group III) one of whom had a familial predisposition.



symptoms 1 respiratory abnormalities 2 locally convulsions 3. fever 4. irritability 5. rigidity

Fig. 3

Incidence of neonatal symptoms in 122 patients dying in the neonatal period, the main cause of death being

1. pulmonary stelektasis (normal brain).
2. pulmonary stelektasis and cerebral oedema.
3. pulmonary stelektasis, intracranial haemorrhage ± cerebral oedema.
4. intracranial haemorrhage ± cerebral oedema (normal lungs).

CHAPTER III

The diagnostic significance of neonatal symptoms based on autopsy findings in patients dying in the neonatal period

The 122 patients who died neonatally were, as already mentioned, classified according to the principal cause of death as revealed by postmortem examination viz 1) pulmonary atelectasis, normal brain, 2) pulmonary atelectasis and cerebral oedema, 3) pulmonary atelectasis and cerebral haemorrhage \pm cerebral oedema, and 4) cerebral haemorrhage \pm cerebral oedema, normal lungs.

The following analysis aims at demonstrating differences in the symptomatology of the respective groups that would make it possible to distinguish clinically between infants with cerebral damage and infants with normal brains.

Fig. 3 shows the frequency of each symptom within the four groups.

The most striking feature is the total absence of convulsion tremor irritability and rigidity in Group 1

Because of the small size of this group it has been supplemented as follows. 1) all infants dying neonatally at the DPGs from 1957 to 1964 who were found at autopsy to have pulmonary atelectasis and normal brain, a total of 16 cases 2) a total of 10 infants dying neonatally at the University Hospital (Rigshospitalet = RH) from 1961 to 1964 in whom autopsy performed at the Department of Pathology of the RH had revealed pulmonary atelectasis as the sole pathological abnormality. Informations were extracted from the clinical records of these children similarly to those of the original material. The clinical data on infants dying at the RH were obtained from the records of the Departments of Obstetrics A and B where the infants had been admitted and seen by paediatricians.

This enlarged the series to the more acceptable total of 46 cases, though the group of mature infants remained very small and the preponderance of premature became even larger. The outcome is given in Fig. 4. The fact that this enlarged group also failed to exhibit convulsion tremor irritability and rigidity supports the theory of a specific cerebral origin for these symptoms. In all other groups they occurred with fairly consistent frequency.

As seen from Fig. 3 the frequency of each symptom is essentially the

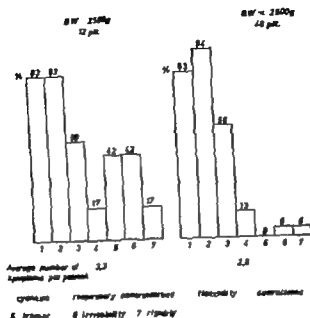


Fig. 5

Incidence of neonatal symptoms in the enlarged material comprising 60 patients dying in the neonatal period, the main causes of death being pulmonary atelectasis and cerebral oedema.

Even though the symptoms of convulsion, tremor, irritability and rigidity seem to be specific to cerebral damage, several patients may have brain damage, perhaps proving fatal, without exhibiting any of these symptoms.

TABLE 11

The time of onset of convulsion in 102 (143) patients dying neonatally and exhibiting pathological findings on brain section
(Figures in parentheses indicate enlarged material)

Autopsy findings	No. pat.	No. of patients with convulsions	
		From 1st day	Only after 1st day
Cerebral oedema + pulmonary atelectasis	19 (60)	1 (2)	2 (6)
Cerebral haemorrhage ± oedema + pulmonary atelectasis	61	7	7
Cerebral haemorrhage ± oedema, normal lungs	22	4	2
Total	102 (143)	12 (13)	11 (15)

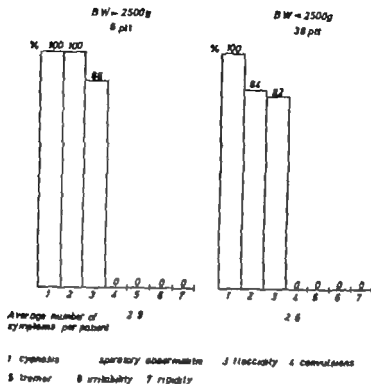


Fig 4

Incidence of neonatal symptoms in the enlarged material comprising 46 patients dying in the neonatal period, the main cause of death being pulmonary atelectasis.

same in the group with cerebral oedema as in those with cerebral haemorrhage \pm cerebral oedema. Here, too the former group was very small and consequently was enlarged—in the same manner as mentioned above—by including 29 patients from DPGs and 12 patients from the obstetric departments A and B and the Dept. of Pathology at the RH. Brain section was performed by Dr Inge Tygstrup. The group then amounted to 60 infants, of whom 12 were mature. The distribution of the symptoms can be seen in Fig 5. Making allowance for the small number of mature patients the trend is unchanged, with the same symptoms occurring with equal frequency in cases with cerebral oedema and in those with cerebral haemorrhage.

The time of onset of convulsions is of no particular help in making a differential diagnosis because of the rarity of this symptom in the group (see Table 11). In cases with cerebral haemorrhage about half the convulsions started within the first 24 hours of birth, the remainder did not begin until the second day or later. When cerebral oedema occurred in the absence of haemorrhage, there was a tendency towards late onset, however in some cases the convulsion did in fact begin on the first day.

Among the 50 full-term infants with cerebral damage 23 or 46 per cent. had presented only cyanosis, respiratory disorders and flaccidity in varying combinations. The corresponding figures in premature infants with cerebral damage were 41 or 79 per cent.

As seen from Table 12 this relationship is essentially the same whether cerebral oedema or cerebral haemorrhage is present. A substantial proportion of these children, notably among the premature, will present the same symptoms as those dying from pulmonary atelectasis.

The question is, therefore, whether it is possible to make a clinical distinction between the two groups.

The form in which cyanosis occurs seems to offer a guide. In Table 13 the three groups presenting pathological brain findings have been listed together. Cyanotic attacks seem to be somewhat more frequent among the patients with cerebral damage; however since this form is seen frequently also in the absence of cerebral damage, it is of no diagnostic value. The same may be said "with opposite sign" of permanent cyanosis, which is more frequent in isolated pulmonary atelectasis.

If, however the time of onset of cyanotic attacks is considered—whether occurring during the first 24 hours of birth or not until the second day of life or later—a difference becomes evident (Table 14). Delayed onset of cyanotic attacks is seen only in cases with cerebral damage and was observed in about one-fifth of that group.

Similarly a comparison has been made between cyanosis in mature and premature infants as well as between infants with cerebral oedema and with cerebral haemorrhage. No differences were demonstrated (see Tables 15, 16 and 17) with the exception of a preponderance of cyanotic attacks of early

TABLE 15
Forms of cyanosis in 122 (189) patients dying in the neonatal period. Patients are grouped according to BW
(Figures in parentheses indicate the enlarged series)

Autopsy findings		No. pat.	Cyanotic attacks	Permanent cyanosis
BW > 2500 g	Pulmonary atelectasis			
	Normal brain	5 (8)	2 (5) pat.	3 (3) pat.
	Pathological brain ± pulmonary atelectasis	50 (53)	62 % (62 %)	22 % (21 %)
BW < 2500 g	Pulmonary atelectasis			
	Normal brain	15 (38)	40 % (37 %)	60 % (63 %)
	Pathological brain ± pulmonary atelectasis	32 (90)	50 % (55 %)	37 % (28 %)

TABLE 12

Neonatal symptoms in 102 infants dying neonatally with pathological findings at brain section

Autopsy findings	BW > 2500 g		BW < 2500 g		Total
	Without specific symptoms	With specific symptoms	Without specific symptoms	With specific symptoms	
Pulm. atelectasis + cerebral oedema	4	5	9	1	19
Pulmonary atelectasis + cerebral haemorrhage ± cerebral oedema	13	14	25	9	61
Cerebral haemorrhage ± cerebral oedema, normal lungs	6	8	7	1	22
Total	23	27	41	11	102

TABLE 13

Forms of cyanosis in 122 (189) infants dying during the neonatal period (Figures in parentheses indicate the enlarged material)

Autopsy findings	No. pat.	Cyanotic attacks	Permanent cyanosis
Pulmonary atelectasis			
normal brain	20 (46)	40 % (41 %)	60 % (59 %)
Pathological brain ± pulmonary atelectasis	102 (143)	56 % (57 %)	27 % (25 %)

TABLE 14

The time of onset of cyanotic attacks in 122 (189) patients dying in the neonatal period (Figures in parentheses indicate the enlarged group)

Autopsy findings	No. pat.	Cyanotic attacks	
		From 1 st day	Late occurrence only
Pulmonary atelectasis			
normal brain	20 (46)	40 % (41 %)	0 (0)
Pathological brain ± pulmonary atelectasis	102 (143)	35 % (29 %)	21 % (28 %)

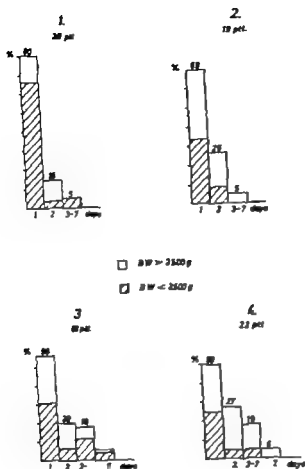


Fig. 6

Tone of neonatal death in 122 patients. 1-4 diagnostic groups as in Fig. 3, p. 59

Here, too, the average number of symptoms per patient was somewhat higher in the mature than in the premature, though with little variation between the respective pathological groups (Figs. 3, 4 and 5)

Conclusion

The diagnosis of cerebral damage in newborn infants is difficult to establish, particularly in the premature, who exhibit very few symptoms.

Convulsion, tremor, irritability and rigidity can, with a degree of certainty be considered specifically cerebral symptoms, being found in the present material only in patients who were found to have cerebral haemorrhages

TABLE 16

*Time of onset of cyanotic attacks in 122 (189) patients dying in the neonatal period.
Patients grouped according to BW
(Figures in parentheses indicate the enlarged series)*

Autopsy findings		No. pat.	Cyanotic attacks	
			From 1 st day	Late occurrence only
BW > 2500 g	Pulmonary atelectasis			
	Normal brain	5 (8)	2 (5) pat.	0 (0) pat.
	Pathological brain			
	± pulmonary atelectasis	50 (53)	34 % (34 %)	28 % (28 %)
BW < 2500 g	Pulmonary atelectasis			
	Normal brain	15 (38)	40 % (37 %)	0 (0) pat.
	Pathological brain			
	± pulmonary atelectasis	52 (90)	37 % (27 %)	13 % (28 %)

TABLE 17

Form of cyanosis and time of onset of cyanotic attacks in the enlarged series of 143 patients dying in the neonatal period and revealing pathological findings on brain section

Autopsy findings	No. pat.	Cyanotic attacks	Permanent cyanosis
Cerebral oedema	60	57 %	27 %
Cerebral haemorrhage ± oedema	83	59 %	24 %

	No. pat.	Cyanotic attacks	
		From 1 st day	Late occurrence only
Cerebral oedema	60	23 %	33 %
Cerebral haemorrhage ± oedema	83	34 %	24 %

onset in cerebral haemorrhage and delayed onset in cerebral oedema, a trend with no obvious practical implications.

Permanent cyanosis in all cases developed within 24 hours of birth.

The large majority of neonatal fatalities occurred within 24 hours of birth, more often in cases with isolated pulmonary atelectasis. In cases of cerebral haemorrhage the patients survived somewhat longer with about one quarter dying later than the third day and some as late as the second week of life. Only a small percentage in the groups with pulmonary atelectasis and with pulmonary atelectasis as well as cerebral oedema survived the third day and one survived the first week. (See Fig. 6)

CHAPTER IV

The significance of neonatal symptoms in the immediate prognosis

In the following pages an attempt is made to detect neonatal symptoms or groups of symptoms that may offer a clue to the prognosis for immediate survival.

Fig. 7 illustrates the incidence of individual symptoms in the infants who survived the neonatal period compared with those who died.

It is evident that in the entire group as well as in the two weight groups an appreciable majority of the patients who died exhibited cyanosis, respiratory disorder and flaccidity. In this respect there is no difference between mature and premature infants.

The remaining symptoms are slightly more frequent in the survivors than in the infants who died, whether mature or premature. Here again the mature, whether surviving or not, exhibited more of these symptoms than the premature.

The average number of symptoms per patient was somewhat lower in the survivors, viz. 2.5 in the mature compared with 3.1 in those who died. The corresponding figures for the premature were 1.7 and 2.5. Thus on average the premature in each group presented fewer symptoms than the mature.

Cyanosis, the commonest symptom, was present in 208 patients. Half of these survived prematurity however plays an important role, since 74 per cent of the premature and only 36 per cent of the mature with cyanosis died during the neonatal period (see Table 18). This table also shows the mortality rates for the different forms of cyanosis subdivided according to time of onset and duration.

Permanent cyanosis persisting beyond the first few hours of life seems to indicate a poor prognosis for survival in mature as well as premature patients.

Cyanotic attacks occurred in 77 per cent of the cases, somewhat more often in the mature. Its occurrence during the first day of life apparently is a less favourable sign in the premature than in the mature.

or cerebral oedema at autopsy. These symptoms were rare in the premature infants.

Brain damage may be present in a large number of cases, especially among the premature, in which cyanosis, respiratory disorder or flaccidity are the only clinical features.

The onset of cyanotic attacks after the first 24 hours of life suggests cerebral damage.

Clinical findings are not conclusive in differentiating between cerebral oedema and cerebral haemorrhage.

The principal point at which the above conclusion diverges from that of previous authors concerns the statement that convulsion, tremor, irritability and rigidity are specific cerebral symptoms. Many authors (*Clein* 1929 *Grille* 1936 *Liebs* 1940 *Peterman* 1946 *Bound* 1956 *Illingworth* 1957 *Ahvenainen* 1956-59 and *Craig* 1960) have found convulsion in extra-cerebral conditions, although it was reported to be more frequent in cerebral disorders (*Peterman* 1946 *Ahvenainen* 1958 and *Craig* 1960). The main reason for this discrepancy may be the method of selection in the present study which excludes in advance many conditions that may cause convulsion.

Otherwise the results are in agreement with those of previous writers. This applies to the general difficulties in establishing a definite diagnosis as well as the impossibility of distinguishing clinically between cerebral oedema and cerebral haemorrhage (*Seltz* 1907 *Esch* 1916 and *Craig* 1960). The relative scarcity of specifically cerebral symptoms in the premature is also in accord with the findings of previous authors (*Heldler* 1927 *Bound* 1956 *Znamenacek* 1957 and *Craig* 1960).

TABLE 18

Forms of cyanosis and mortality in 208 newborn infants

Cyanosis	Total	131 patients BW > 2500 g		77 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Permanent, a few hours	8	7	1	0	0
Permanent, within 1st day	38	2	12	0	24
Permanent, 1st and following days	2	0	1	0	1
Attacks, 1st day	84	37	14	9	24
Attacks, 1st and following days	38	27	5	5	1
Attacks, later than 1st day only	38	11	14	6	7
Total	208	84	47 (36 %)	20	57 (74 %)

Delayed onset of cyanotic attacks, i.e. after the first 24 hours of life, seems, in the mature, to imply a worse prognosis than earlier onset.

Cyanosis here has been considered on its own. It must, however, be borne in mind that in the great majority of cases this feature was accompanied by other symptoms.

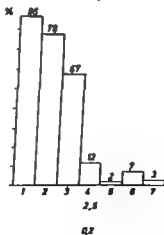
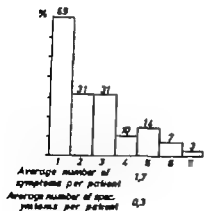
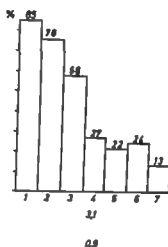
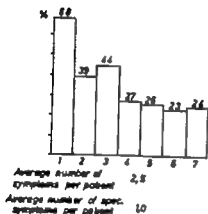
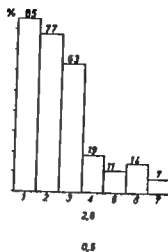
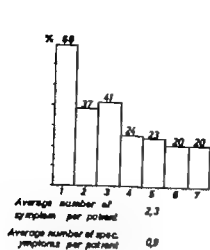
As already mentioned, 22 patients presented cyanosis as the only symptom. As seen from Table 19 monosymptomatic cyanosis always was attack wise, and three of the 22 patients died neonatally. The mortality rate is equal in the two weight groups, and considerably lower than in the group with cyanosis in combination with other symptoms. In the latter group, which comprises 186 patients (208 minus 22) the mortality rate among the mature was 39 per cent, in the premature the rate was 80 per cent.

Respiratory abnormalities were present, as the next commonest feature, in 152 patients, of whom only three had no additional symptoms. All three were born at term: none had periodic apnoea, all survived the neonatal period. The mortality rate among the remaining 149 patients, who had

TABLE 19

Monosymptomatic cyanosis in 22 newborn patients

Cyanosis	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Permanent	0	0	0	0	0
Attacks, first day	14	9	2	2	1
Attacks, 1st & following day	4	3	0	1	0
Attacks, later than 1st day only	4	1	0	3	0
Total	22	13	2	6	1



1 cyanosis 2 respiratory abnormalities 3 floccidity 4 overstimulation 5 tremor 6 irritability 7 rigidity

Fig 7

Incidence of neonatal symptoms in patients surviving (left column) and dying during the neonatal period (right column).

Upper part: the total material.

Middle: patients with BWs over 2500 grams.

Lower part: patients with BWs below 2500 grams.

TABLE 22

Convulsion in 38 newborn patients presenting additional symptoms

Convulsion	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
During first day	19	9	6	0	4
During 1 st and following days	9	7	2	0	0
Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the first 24 hours of life or later, apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and *rigidity* occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of premature patients presenting these symptoms was too small to be prognostically conclusive.

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20-30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally.

Combinations of symptoms were numerous, however, as might be expected,

TABLE 23

Mortality rates in newborn patients with non-specific symptoms only

Neonatal symptoms	No	% of all 275 pts.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir. disorder	47	17 %	11	13	54 %	5	18	78 %
Cyanosis + flaccidity	23	8 %	10	2	17 %	1	9	82 %
Respir. disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir. disorder + flaccidity	49	18 %	13	10	42 %	1	14	96 %
	124	45 %	36	26		8	34	
			62 = 35 % of 179			62 = 63 % of 96		

TABLE 20

Respiratory disorders in 149 newborn infants presenting additional symptoms

Respiratory disorder	Total	87 patients BW > 2500 g		62 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Difficult, grunting	97	39	22	10	46
Periodic apnoea	33	6	14	0	13
Difficult, grunting and periodic apnoea	19	0	6	0	13
Total	149	45	42 (48 %)	10	52 (84 %)

additional symptoms, was 63 per cent, higher in the premature (84 per cent) than in the mature (48 per cent) the difference between the weight groups was much the same as in the cyanotic patients, though with a relatively higher mortality in the mature.

The respiratory disorders consisted of either difficult, grunting and somewhat irregular respiration as the most common form in each weight group or of periodic apnoea or both.

As may be seen from Table 20 periodically apnoeic respiration or respiration that was also difficult suggested an unfavourable prognosis for life in mature as well as in premature patients. Grunting respiration on its own appeared to be a more ominous sign in the premature than in the mature.

Flaccidity which was next in frequency occurred in 140 patients, or in about half of both weight groups. As an isolated symptom it was present in 8 patients, or four in each group. Of these one premature infant died. In the remaining 132 cases 39 per cent of the mature and 88 per cent of the premature died (Table 21). The figures thus parallel those found for the two aforesaid symptoms.

Convulsion was present in 60 patients. As already mentioned its frequency was equal in surviving and fatal cases within the two weight groups. In the premature, convulsion when occurring with other symptoms, was associated with a mortality rate as high as 73 per cent as against 32 per cent in the mature (see Table 22).

TABLE 21

Flaccidity in 132 newborn patients presenting additional symptoms

	Total	82 patients BW > 2500 g		50 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Flaccidity	132	50	32 (39 %)	6	44 (88 %)

TABLE 22

Convulsion in 58 newborn patients presenting additional symptoms

Convulsion	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
During first day	19	9	6	0	4
During 1st and following days	9	7	2	0	0
Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the first 24 hours of life or later apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and rigidity occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of premature patients presenting these symptoms was too small to be prognostically conclusive.

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20-30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally.

Combinations of symptoms were numerous however as might be expected,

TABLE 23

Mortality rates in newborn patients with non-specific symptoms only

Neonatal symptoms	No.	% of all 223 pat.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	47	17 %	11	11	54 %	5	18	78 %
Cyanosis + flaccidity	23	8 %	10	2	17 %	2	9	82 %
Respir disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir disorder + flaccidity	49	18 %	14	10	42 %	1	24	96 %
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Periodic apnoea	33	6	14	0	13
Difficult, grunting and periodic apnoea	18	0	6	0	13
Total	149	45	42 (48 %)	10	52 (84 %)

additional symptoms, was 63 per cent, higher in the premature (84 per cent) than in the mature (48 per cent) the difference between the weight groups was much the same as in the cyanotic patients, though with a relatively higher mortality in the mature.

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As may be seen from Table 20 periodically apnoeic respiration or respiration that was also difficult suggested an unfavourable prognosis for life in mature as well as in premature patients. Grunting respiration on its own appeared to be a more ominous sign in the premature than in the mature.

Flaccidity which was next in frequency occurred in 140 patients, or in about half of both weight groups. As an isolated symptom it was present in 8 patients, or four in each group. Of these one premature infant died. In the remaining 132 cases 39 per cent of the mature and 88 per cent of the premature died (Table 21). The figures thus parallel those found for the two aforesaid symptoms.

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Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the first 24 hours of life or later apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and rigidity occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of premature patients presenting these symptoms was too small to be prognostically conclusive.

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20-30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally.

Combinations of symptoms were numerous however as might be expected,

TABLE 23

Mortality rates in newborn patients with non-specific symptoms only

Neonatal symptoms	No.	% of all 273 pts.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir. disorder	47	17 %	11	13	54 %	5	18	78 %
Cyanosis + flaccidity	3	8 %	10	2	17 %	2	9	82 %
Respir. disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir. disorder + flaccidity	49	18 %	14	10	42 %	1	4	96 %
	124	45 %	36	26		8	34	
			62 = 35 % of 179			62 = 65 % of 96		

TABLE 24

Mortality rates in newborn infants presenting two or three non-specific symptoms co-existent with one or more additional symptoms

Neonatal symptoms	No.	BW > 2500 g			BW < 2500 g		
		Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	82	27	24	47 %	3	28	90 %
Cyanosis + flaccidity	81	29	24	45 %	3	26	90 %
Respir disorder + flaccidity	76	22	23	51 %	3	28	90 %
Cyanosis + respir disorder + flaccidity	18	6	10	63 %	1	1	(50 %)

the commonest included cyanosis, respiratory disorder and flaccidity Table 23 shows the mortality rate in the cases where these symptoms occurred in the absence of specific cerebral symptoms. 45 per cent of all the 275 patients belonged in these groups, considerably more (65 per cent) premature than mature infants (35 per cent) Table 24 gives mortality rates for the same combinations co-existent with other symptoms.

Conclusion

As might be expected permanent cyanosis persisting for more than a few hours and periodic apnoea are unfavourable omens for survival in mature as well as premature infants.

Cyanotic attacks within the first 24 hours of life, difficult and grunting respiration, flaccidity and convulsion are also of serious prognostic significance in the premature newborn, but less so in the mature. Combinations of the non-specific features, cyanosis, respiratory disorder and flaccidity are also poor prognostic signs in premature infants.

In mature neonates the onset of cyanotic attacks after the first day of life implies a more unfavourable prognosis than onset within the first 24 hours.

The specific cerebral symptoms—convulsion, tremor irritability and rigidity—with the exception of convulsions in the premature, seem to have less serious implications for the immediate prognosis.

An increasing number of symptoms means a decreasing chance of survival. However death occurred in mature as well as premature infants who presented only one neonatal symptom.

CHAPTER V

The significance of neonatal symptoms in long term prognosis

The eventual progress of the surviving children as already mentioned differed greatly. In the following pages a comparison is made between neonatal symptoms in those infants who later exhibited severe, minor or possible cerebral sequelae and those who developed normally. The aim has been the assessment of possible symptomatological differences during the neonatal period that might give a reliable indication of the long-term prognosis.

Fig. 8 shows the incidence of neonatal symptoms in mature and premature patients in the Groups I-IV presented in Chapter II (divided according to decreasing degrees of severity with Group IV being normal)

Since the premature groups are very small, all calculations concerning these groups must be treated with reservation.

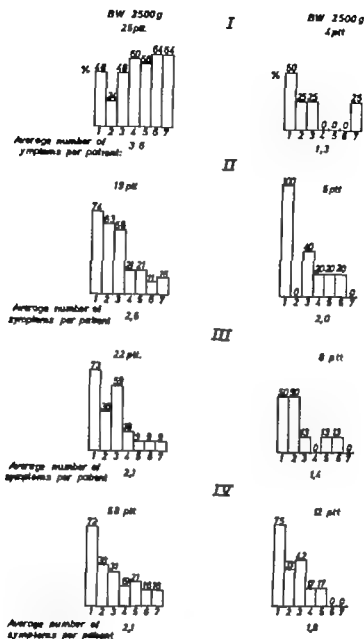
The most conspicuous difference is the higher incidence of convulsion, tremor, irritability and rigidity in the mature infants in Group I compared with all other groups. 23 patients, or 92 per cent in this group exhibited one or more of these symptoms. The corresponding percentage for mature children in the other groups was about 40. In the premature groups the overall percentage was about 25.

The average number of symptoms per patient decreased gradually from Groups I to IV being, respectively 3.6, 2.6, 2.1 and 2.1. In the premature the figures, without showing distinctive trends, were lower viz. 1.3, 2.0, 1.4 and 1.8 symptoms per patient, respectively.

The symptomatological combinations were so numerous that the same combination occurred only in few cases. An attempt to establish the prognosis for all combinations would have practically decimated the material.

The approach has been as follows.

- 1) to determine whether any one symptom occurring on its own might give definite indications of the long-term prognosis, and subsequently to similarly evaluate groups of patients exhibiting a combination of
- 2) two or three non-specific symptoms,
- 3) one non-specific and one specific symptom,
- 4) two specific symptoms.



1. cyanosis 2. respiratory abnormalities 3. floccidity 4. convulsions 5. tremor 6. irritability 7. rigidity

Fig 3

Incidence of neonatal symptoms in patients surviving the neonatal period.

I Patients with severe cerebral sequelae.

II Patients with minor cerebral sequelae.

III Patients with mild deviations of presumably cerebral origin.

IV Patients with later normal development.

Finally an evaluation has been made of those children who presented the same symptoms as those in the last three groups in combination with one or more additional symptoms.

1 Patients with only one neonatal symptom

As already mentioned a single symptom was found in 37 patients. Of these 32 survived the neonatal period. Table 25 shows their later fate. The groups are small and allow no definite conclusions. However, it should be noted that the specific symptoms seldom occurred on their own, and not at

TABLE 25

The relationship between neonatal symptoms and later condition in the presence of one symptom only

Neonatal symptoms	BW > 2500 g 23 patients					BW < 2500 g 9 patients				
	Total	I	II	III	IV	Total	I	II	III	IV
Cyanosis	13	1		2	10	6	1	2	1	2
Respir. disorder	3		2		1	0				
Flaccidity	4		1	2	1	3			1	2
Convulsion	2	1			1	0				
Irritability	1			1		0				
Pat. with only one non-specific sympt.	20	3	15	5	20	6				
All pat. regardless of BW with 1 non-specific sympt. only	29	7	17	5	21	5				

TABLE 26

Relationship between neonatal symptoms and later condition in the presence of two or three non-specific symptoms

Neonatal symptoms	BW > 2500 g 26 patients					BW < 2500 g 8 patients				
	No.	I	II	III	IV	No.	I	II	III	IV
Cyanosis + respir. disorder	11		3		8	5	1		2	2
Cyanosis + flaccidity	10	1	2	2	5	2		2		
Respir. disorder + flaccidity	1				1	0				
Cyanosis + respir. disorder + flaccidity	14		4	7	3	1				1
BW > 2500 g	36	3	25	25	47					
All patients in both weight groups	44	3	25	23	45					

all in the premature. Convulsion as well as irritability were found on their own in a few mature children, and were not invariably indicative of a poor prognosis. Cyanosis, which was the commonest single symptom, most often implied a favourable prognosis.

2. Patients with two or three non specific symptoms

The later fate of infants showing two or three non specific symptoms apparently did not differ from those who exhibited only one unspecific symptom (see Tables 25 and 26). The distribution within Groups I-IV in the latter group taken as a whole, was 7 17 21 and 55 per cent and in the former 5 25 25 and 45 respectively

3 Patients with one specific and one non-specific symptom

This combination was found in only a small number of cases. Table 27 gives the figures, from which it can be seen that the presence of one specific plus one non-specific symptom from a prognostic point of view equals the presence of non-specific symptoms only

TABLE 27
Relationship between neonatal symptoms and later condition in the presence of one specific plus one non specific symptom

Neonatal symptoms	BW > 2500 g 8 patients					BW < 2500 g 3 patients				
	Follow-up groups									
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + cyanosis	3			2	1	1				1
Convulsion + flaccidity	1		1							
Tremor + cyanosis					2	1				1
Irritability + respir disorder	0					1			1	
Irritability + flaccidity	1	1				0				
Rigidity + cyanosis	1				1	0				
All patients in both weight groups	11	1	1	3	6					

4 Patients with two specific symptoms

This combination was seldom found in the mature and not at all in the premature (see Table 28). The figures do not allow any conclusion to be drawn but suggest a tendency towards a more unfavourable prognosis: three of the eight patients are found in Group I however the likelihood of a normal development exists.

These four groups comprise well over half the mature (75) and about two-thirds (20) of the premature infants surviving the neonatal period.

TABLE 28

The relationship between neonatal symptoms and later condition in the presence of two specific symptoms

Neonatal symptoms	BW > 2500 g 8 patients Follow-up groups				
	No.	I	II	III	IV
Convulsion and tremor	1	1			
Convulsion and rigidity	3	1		2	
Tremor and irritability	2				2
Tremor and rigidity	1	1			
Irritability and rigidity	1				1
Total	8	3	0	2	3

In the following, consideration is given to those patients who presented the same combinations of symptoms as the last three groups plus one or more additional features, whether specific or not.

Table 29 illustrates the relationship between later condition and the presence of no less than three neonatal symptoms, of which at least two are non-specific. A comparison with Table 26, where only two or three non-specific symptoms were present, suggest that the risk of a more unfavourable course increases proportionally with the number of symptoms.

TABLE 29

Relationship between neonatal symptoms and later condition in the presence of two or three non-specific symptoms plus one or more additional symptoms

Neonatal symptoms	BW > 2500 g					BW < 2500 g				
	No.	I	II	III	IV	No.	I	II	III	IV
Cyanosis + respir. disorder	27	4	7	8	8	3			1	2
Cyanosis + flaccidity	29	5	6	9	9	3				3
Flaccidity + respir. disorder	22	3	6	7	6	3	1			2
Cyanosis + respir. disorder + flaccidity	6	2	2		2	1				1
BW > 2500 g		15— 20 %			30 %					

Table 30 lists combinations of one specific, one non-specific together with at least one additional symptom. A comparison with Tables 27 and 29 reveals that in the presence of at least three symptoms the prognosis is appreciably worse if at least one of the three is specific than if, in the presence of two symptoms, one is specific.

all in the premature. Convulsion as well as irritability were found on their own in a few mature children and were not invariably indicative of a poor prognosis. Cyanosis, which was the commonest single symptom, most often implied a favourable prognosis.

2 Patients with two or three non-specific symptoms

The later fate of infants showing two or three non-specific symptoms apparently did not differ from those who exhibited only one unspecific symptom (see Tables 25 and 26). The distribution within Groups I-IV in the latter group taken as a whole, was 7 17 21 and 55 per cent and in the former 5 25 25 and 45 respectively.

3 Patients with one specific and one non-specific symptom

This combination was found in only a small number of cases. Table 27 gives the figures, from which it can be seen that the presence of one specific plus one non-specific symptom from a prognostic point of view equals the presence of non-specific symptoms only.

TABLE 27
Relationship between neonatal symptoms and later condition in the presence of one specific plus one non specific symptom

Neonatal symptoms	BW > 2500 g 8 patients					BW < 2500 g 3 patients				
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + cyanosis	3			2	1	1				1
Convulsion + flaccidity	1		1							
Tremor + cyanosis	2				2	1				1
Irritability + respir disorder	0					1			1	
Irritability + flaccidity	1	1				0				
Rigidity + cyanosis	1				1	0				
All patients in both weight groups	11	1	1	3	6					

4 Patients with two specific symptoms

This combination was seldom found in the mature and not at all in the premature (see Table 28). The figures do not allow any conclusion to be drawn but suggest a tendency towards a more unfavourable prognosis. three of the eight patients are found in Group I however the likelihood of a normal development exists.

These four groups comprise well over half the mature (75) and about two-thirds (20) of the premature infants surviving the neonatal period.

These figures apply to the mature patients.

The small size of the premature groups makes an evaluation very difficult; however, it should be noted that even in the presence of as many as three neonatal symptoms, where one or two are specific, this need not indicate an unfavourable prognosis for the premature.

The prognostic significance of various forms of cyanosis

Table 32 gives the relationship between later condition and cyanosis in its various forms, either occurring alone or in association with other symptoms.

Cyanosis occurring within the first few hours of life was found exclusively in association with other symptoms and was usually compatible with a good prognosis.

Permanent cyanosis was seen in only two patients surviving the neonatal period. In each case it subsided within the first 24 hours of life and was associated with other symptoms. One of the patients is found in Group I, the other in Group IV.

The figures in Table 32 apparently do not allow prognostic differentiation between cases where cyanotic attacks subsided within the first 24 hours of life and those where they persisted for several days.

Among the 52 cases with cyanotic attacks persisting over the first few days, 19 patients had recurrent attacks over two to four days, while in the remaining 13 cases the duration was five days or more. Of these 13 cases four were placed in Group I and four in Group IV while of the first

TABLE 32
Relationship between later condition and various forms of cyanosis

Monosymptomatic cyanosis			Follow-up groups										
			BW > 2500 g					BW < 2500					
			No.	I	II	III	IV	No.	I	II	III	IV	
Attacks	from 1st day	for 1 day	9	1		1	7	2					2
		> 1 day	3			1	2	1		1			
	only after 1st day	for 1 day	1				1	1				1	
		> 1 day	0					2	1	1			
Cyanosis plus other symptoms													
Within the first few hours			7	1		4	2	0					
Persistent after 1st day			2	1			1	0					
Attacks	from 1st day	for 1 day	28	4	7	4	13	7		1	2	4	
		> 1 day	4	3	3	6	12	4	1	1	1	1	
	only after 1st day	for 1 day	4		2		2	3		1			2
		> 1 day	6	2	2		2	0					

TABLE 30

Relationship between neonatal symptoms and later condition in the presence of one specific plus one non-specific plus one or more other symptoms

Neonatal symptoms	Follow-up groups									
	BW > 2500 g					BW < 2500 g				
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + cyanosis	16	7	3		6	2		1		1
Convulsion + respiratory abnormality	9	3	2		4					
Convulsion + flaccidity	9	4	1		4	1				1
Tremor + cyanosis	16	7	3	2	4	3		1	1	1
Tremor + respiratory abnormality	11	4	2	1	4	2			1	1
Tremor + flaccidity	11	6	2	1	2	1				1
Irritability + cyanosis	11	7	1	1	2	1		1		
Irritability + respiratory disorder	10	5	1		4					
Irritability + flaccidity	12	8	1	1	2					
Rigidity + cyanosis	15	7	3		5					
Rigidity + respiratory abnormality	9	4	1		4	1	1			
Rigidity + flaccidity	10	7			3	1	1			
BW > 2500 g		40-60 %			20-40 %					

Table 31 shows the same relationship in the presence of at least three neonatal symptoms, where two are specific. The prognosis is usually poor with 60-80 per cent being placed in Group I and is worse than in the case of two specific symptoms occurring alone or in one specific together with two non-specific symptoms (see Tables 28 and 30)

TABLE 31

The relationship between neonatal symptoms and later condition in the presence of two specific plus one or more additional symptoms

Neonatal symptoms	Follow-up groups									
	BW > 2500 g					BW < 2500 g				
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + tremor	14	8	1		5	1		1		
Convulsion + irritability	13	11	1		1	1		1		
Convulsion + rigidity	14	9	2		3	0				
Tremor + irritability	14	10	2		2	1		1		
Tremor + rigidity	14	9	2		3	0				
Irritability + rigidity	14	12	1		1	0				
BW > 2500 g		60-80 %			10-20 %					

The duration of the convulsions, whether of early or late onset, seems to offer a clue to the prognosis. Of seven children who had convulsions from the first day of life the two in Group I exhibited this symptom for respectively five days and beyond two months, the remaining for two or three days only. In six of the seven children in Group I, who had delayed convulsions lasting for more than 24 hours, the symptom persisted for 3-5 days (in the 7th for 2 days) while all others had seizures for two or three days.

In the one patient in Group IV with late onset of convulsion as the only symptom, the symptom persisted for three days.

Cyanotic attacks developing after the first 24 hours of birth invariably began on the second or third day. This was true in two-thirds of the infants who developed convulsions. In the remaining one-third, convulsions developed from one to three weeks after birth. There was no correlation between time of onset, and duration of the convulsions or the severity of sequelae.

Conclusion

Neuro patients

A fairly good prognosis is likely in the presence of

- 1) one neonatal symptom, whether specific or non-specific, or
- 2) two symptoms, even though one is specific, or
- 3) three non-specific symptoms.

Severe cerebral sequelae have been found in less than 10 per cent of such cases, and a perfectly normal development was found in about 50 per cent—or 75 per cent if Group III with questionable sequelae is included.

- 4) The presence of two specific symptoms seems to imply a worse prognosis, with about 30 per cent risk of severe cerebral sequelae.
- 5) With a combination of no less than three symptoms, at least one of which is specific, the prognosis is poorer with a 40-60 per cent risk of severe cerebral sequelae.
- 6) At least three symptoms including two specific ones usually indicate a poor prognosis with a 60-80 per cent risk of severe cerebral sequelae.
- 7) Cyanotic attacks in association with other symptoms developing within the first day of life are found to be an unfavourable prognostic sign when persisting for more than four days. If cyanotic attacks begin later than the first day of life, a duration beyond only two days, seems to imply a poor prognosis.
- 8) Convulsion, which very rarely occurred on its own, seems to indicate a poor prognosis in a great proportion of cases, even if limited to 24 hours. However convulsion lasting for two or three days may be compatible with a good prognosis. If the duration exceeds three days, the outlook appears graver.

mentioned 19 cases none were found in Group I and 10 in Group IV. Of the four infants who had cyanotic attacks as the sole symptom during the first few days, only one (from Group IV) had attacks for as long as 5 days; in the remaining cases the duration was 2 days only.

As might be expected the time factor influenced the prognosis, though long duration of the symptoms was not always a bad sign.

Late onset of cyanosis, which in those dying within the neonatal period was seen only in association with cerebral haemorrhage or oedema, in the case of the survivors did not apparently indicate a worse prognosis than early cyanosis limited to the first 24 hours of life.

17 patients had delayed cyanotic attacks. In the nine the attacks lasted for 24 hours, in eight for more than 24 hours (between 2 and 4 days, and in one case as long as 20 days). In most cases the onset was on the second or third day of life.

None of these 9 patients are to be found in Group I; five are in Group IV. Among the 8 cases three are in Group I, two in Group IV. Here, too, the importance of the time factor is apparent, while the outlook was grave with early cyanosis persisting for more than four days, this also seemed to be the case with delayed cyanosis lasting for only two days.

The prognostic significance of the time factor in convulsion

Table 33 shows the later course in those groups in which convulsion developed within the first 24 hours or later, divided according to the duration of the seizures.

Allowing for the small numbers in each group it is concluded that convulsion in association with other symptoms, whether occurring early or late, and even when limited to 24 hours, almost certainly implies a poor prognosis.

TABLE 33

Time of onset and duration of neonatal convulsion in relation to later condition

Convulsion + other symptoms		BW > 2500 g								BW < 2500 g			
		Follow-up groups											
		No.	I	II	III	IV	No.	I	II	III	IV		
From 1 st day	for one day	9	4		2	3	0						
	> one day	7	2	2	2	1	0						
Only after 1 st day	for one day	4	1	1		2	3		1			2	
	> one day	12	7	1		4	1						
Convulsion as sole symptom													
Only after 1 st day	for one day	1	1										
	> one day	1				1							

CHAPTER VI

Pre- and perinatal conditions

This chapter deals with conditions during pregnancy and delivery and the immediate postnatal state of the infant. These data are correlated with the neonatal symptoms and later development of the child with a view to assessing whether aetiological variations might influence the diagnostic and prognostic significance of the neonatal symptoms.

Complications of pregnancy

In 33 mothers, or 12 per cent of the cases, a total of 36 complications of pregnancy were reported, as listed in Table 34

TABLE 34
Complications of pregnancy in 33 patients

Toxaemia with hypertension	6
Oedema and albuminuria	4
Hyperemesis	7
Unspecified malaise	4
Vaginal bleeding	4
Hydramnios	4
Miscellaneours	7
Total	36

The hypertension in one of the toxæmic patients probably was nephrogenic: 10 years before delivery a right-sided hydronephrosis had been demonstrated, and an operation on the right ureter had been performed 4 years later. The patient had suffered repeated urinary infections, on the last occasion 10 days before delivery. Her systolic blood pressure purportedly had been 200. Of the other five cases two were mild and three were more severe. In one of these three there had also been vaginal bleeding during the third month of pregnancy.

Premature patients

The evaluation is very difficult, firstly because very few of these infants survived the neonatal period secondly : premature infants usually present very few symptoms, and obviously fewer specific symptoms than the mature. However it should be noted that the presence of as many as three symptoms, including one or two specific symptoms, is not tantamount to a poor prognosis.

TABLE 36

Complications of pregnancy and delivery in 17 patients

Occurrence during pregnancy	Complications of	
	Pregnancy	Delivery
Early (4 patients)	Hyperemesis	Precipitate delivery
	Hypertension	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Gynecologic surgery	Poor heart sound
Late (6 patients)	Toxemia	Placenta praevia
	Toxemia	Premature placental separation
	Toxemia	Forceps delivery
	Toxemia	Prolonged delivery
	Oedema, albuminuria	Prolonged delivery
	Jaundice in VIII	Breech delivery
Throughout (7 patients)	Hyperemesis	Placenta praevia
	Hyperemesis	Prolonged delivery
	Hyperemesis	Prolonged delivery
	General malaise	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Anaemia	Precipitate delivery

The exact duration of the delivery was rarely stated, however a delivery has been classified as prolonged only if it is known to have lasted for more than 24 hours, and as precipitate if its duration was less than two hours.

The abnormal presentations were as follows: breech or breech-footling in seven cases, deep transverse in two cases, transverse in one and anterior vertex in four.

In one case of premature placental separation there was also precipitate delivery and early rupture of membranes. In another such case there was breech presentation. In one case of primary inertia the presentation was anterior vertex, and in two the infant had the cord around the neck.

In 17 out of 33 cases with complications of pregnancy there were also delivery complications (see Table 36). The combinations were numerous. Abnormal deliveries were more frequent in those cases where complications had persisted throughout the pregnancy.

In the much larger group of cases (242) with uncomplicated pregnancy the incidence of delivery complications was 43 per cent.

Asphyxia

As regards the condition of the infants immediately after birth the only reliable information concerns the presence or absence of asphyxia.

Asphyxia, as already mentioned, is defined here as delayed establishment

Four mothers had oedema and albuminuria in the presence of normal blood pressure. Two of these also had hyperemesis

A total of seven mothers had hyperemesis, three during the first half, four throughout the pregnancy

Vaginal bleeding occurred in four cases in three during the third month, the fourth had spot bleeding throughout the pregnancy

Four had hydramnios, the degree of which had not been stated. One was known to have developed acutely during the last weeks of pregnancy

"Miscellaneous" comprises three early and three late complications as well as one case of unspecified anaemia, which persisted throughout the pregnancy. The early complications comprised two cases of minor gynaecological surgery during the first and second month (excision of a cyst of the corpus luteum and of a uterine polyp, respectively). The third mother had rubella during the third month.

The late complications were as follows. In two cases a febrile illness, presumably influenza, immediately before and during the delivery. A third mother had jaundice, unassociated with fever or other symptoms, persisting for two weeks during the eighth month. She had experienced similar conditions during previous pregnancies.

In all, 10 complications were limited to the first half of the pregnancy while 18 occurred in the latter half and eight persisted throughout.

Complications of delivery

In 121 or 44 per cent of the cases, 127 complications of delivery were reported (Table 35). The rate of complications in deliveries taking place outside the home in 1950 was 21.4 per cent in Copenhagen County. Table 35 shows the findings.

TABLE 35
Complications of delivery in 121 patients

		Prolonged delivery	Manual extraction	Forceps delivery	Caesarean section
Abnormal presentation	14	6	—	4	1
Cranio-pelvic disproportion	4	—	—	—	1
Prolonged, uncompl. delivery	48	48	—	15	—
Precipitate delivery	23	—	—	—	—
Primary inertia	7	5	1	2	—
Placenta praevia	3	—	—	—	2
Premature placental separation	4	—	1	—	—
Early rupture of membranes	7	2	—	—	—
Poor foetal heart sound	5	2	1	3	—
Cord around the neck	8	3	1	—	—
Normal (?) delivery	4	—	3	1	—
	127	68	9	27	4

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	Hypertension	Prolonged delivery
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	General oedema	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Anaemia	Precipitate delivery

The exact duration of the delivery was rarely stated, however a delivery has been classified as prolonged only if it is known to have lasted for more than 24 hours, and as precipitate if its duration was less than two hours.

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In all, 10 complications were limited to the first half of the pregnancy while 18 occurred in the latter half and eight persisted throughout.

Complications of delivery

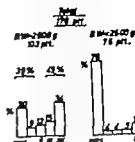
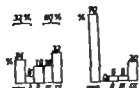
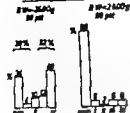
In 121 or 44 per cent of the cases, 127 complications of delivery were reported (Table 35). The rate of complications in deliveries taking place outside the home in 1950 was 21.4 per cent in Copenhagen County. Table 35 shows the findings.

TABLE 35
Complications of delivery in 121 patients

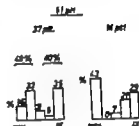
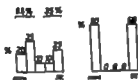
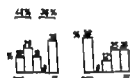
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Prolonged, uncompl. delivery	48	48	2	15	—
Precipitate delivery	23	—	—	—	—
Primary inertia	7	5	1	2	—
Placenta praevia	3	—	—	—	2
Premature placental separation	4	—	1	—	—
Early rupture of membranes	7	2	—	—	—
Poor foetal heart sound	5	2	1	3	—
Cord around the neck	8	3	1	—	—
Normal (?) delivery	4	—	3	1	—
	127	68	9	27	4

No asphyxiaNormal pregnancy
Normal delivery

BW=3400g 30 pct. BW=3500g 30 pct.

Asphyxia of short duration

20 pct. 6 pct.

Asphyxia of longer duration

10 pct. 3 pct.

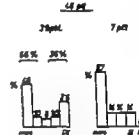
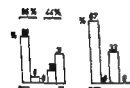


Fig. 9

Relationship between conditions during pregnancy and delivery occurrence of asphyxia and the later conditions of the children.

Mort: Patients dying during the neonatal period.

I. Patients with severe cerebral sequelae.

II. Patients with minor cerebral sequelae.

III: Patients with mild deviations of presumably cerebral origin.

IV: Patients with normal development.

hence only these two have been considered. (The other groups comprised 10 cases or less)

In the following section only mature infants are considered, since the question of prematurity will be dealt with in Chapter VII. The respective groups have been subdivided according to the presence and duration of primary asphyxia on the assumption that any factor which gives rise to

of spontaneous respiration after birth. It was observed in 97 children (35 per cent) These figures however represent an absolute minimum, since the administration of drugs immediately after birth in several additional cases indicated the presence of asphyxia, even though this had not been stated explicitly

These 97 cases have been divided into two groups according to the duration of the asphyxia, with an arbitrary line drawn at 5 minutes. In 51 the asphyxia was of short duration in 46 it was prolonged.

The combinations of the factors mentioned above are shown in Table 37 It will appear that in one-half (138) of the cases there were no complications of pregnancy or delivery or at least no recognized complications. About one-quarter of these exhibited asphyxia, which in half the cases was prolonged.

TABLE 37
Asphyxia related to conditions of pregnancy and birth

Normal pregnancy normal delivery 138 pat.	no asphyxia 100 pat. (72 %)
	+ asphyxia 38 pat. (28 %)
Compl pregnancy normal delivery 16 pat.	no asphyxia 12 pat. (75 %)
	+ asphyxia 4 pat. (25 %)
Normal pregnancy compl. delivery 104 pat.	no asphyxia 58 pat. (56 %)
	+ asphyxia 46 pat. (44 %)
Compl. pregnancy compl. delivery 17 pat.	no asphyxia 8 pat. (47 %)
	+ asphyxia 9 pat. (53 %)

In the small group with complicated pregnancy and normal birth the incidence of asphyxia, including that of long duration, was the same.

Complicated deliveries, as might be expected, were followed by a higher incidence of asphyxia, twice as high as normal deliveries. Again about half the patients had prolonged asphyxia, regardless of the conditions of pregnancy

The influence of pre and perinatal factors on prognosis and neonatal symptoms

The relationship between the course of pregnancy and delivery and the condition at follow up has been analyzed separately in the following combinations. normal pregnancy—normal delivery complicated pregnancy—normal delivery normal pregnancy—complicated delivery abnormal pregnancy—abnormal delivery This subdivision gave a number of fairly small groups. Only the group with normal pregnancy and normal delivery and that with normal pregnancy and complicated delivery were of a fairly acceptable size,

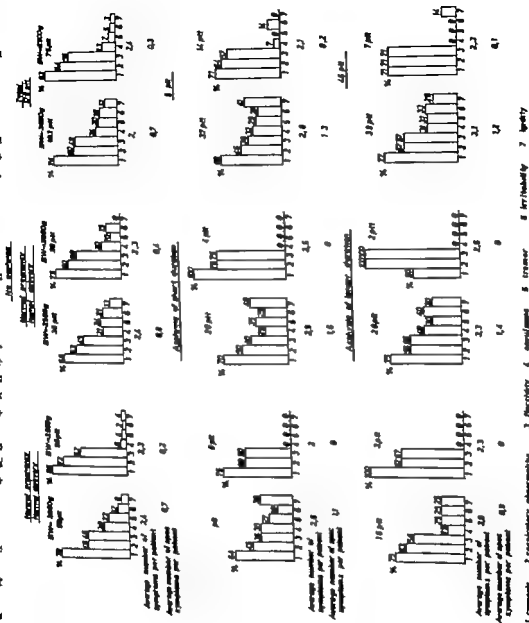


Fig 10 Relationship between conditions during pregnancy and delivery occurrence of asphyxia and neonatal symptoms.

groups—that even in the presence of few (less than three) neonatal symptoms following a normal birth a good prognosis must be made with caution, whereas optimism is more justified when a similar symptomatology follows a complicated birth.

asphyxia as well as neonatal symptoms will have a stronger influence than one that does not precipitate asphyxia. However the resulting groups are so small that the figures must be treated with reserve. Therefore, analyses have also been made for the group as a whole in relation to the presence or absence of asphyxia, regardless of conditions during pregnancy and delivery.

As may be seen from Fig. 9 the course of delivery apparently has no bearing on the prognosis, since the magnitude of the follow up groups is essentially equal whether the delivery was normal or complicated. In contrast, there are in each delivery group far more cases with severe sequelae following brief asphyxia than in the absence of asphyxia and there is a distinctly higher immediate mortality following prolonged asphyxia than in any other group. This seems to support the validity of asphyxia as an indication of the severity of a given influence.

Fig. 10 similarly illustrates the relationships between delivery asphyxia and the incidence of neonatal symptoms. It will appear that brief asphyxia was associated on average with a greater number of symptoms per patient, viz. 2.6 and 2.9 after normal and complicated births, respectively compared with 2.4 in the cases without asphyxia. Moreover specific cerebral symptoms were more frequent following asphyxia. Prolonged asphyxia was followed by a further increase in the average number of symptoms, but some decrease in the frequency of specific symptoms, a relation which, as shown before (p. 7) generally held good for the patients who died in contrast to those who survived, of the high primary mortality following prolonged asphyxia.

The survivors similarly have been separately analysed and correlations were found to be parallel except for the highest incidence of specific cerebral symptoms being found in patients with prolonged asphyxia following a complicated delivery (average of 1.7 symptoms per patient).

The question is whether these variations in the incidence of symptoms may prove of practical prognostic value.

To take two extremes, Table 38 shows the average number of symptoms found in all the full term infants who later exhibited severe cerebral sequelae (Group I) and in all those who developed normally (Group IV). It is apparent that one main group, viz. that of all full-term children in Group I whose delivery had been complicated differs from the remainder in that it exhibits a greater number of symptoms (an average of 4 per cent) and also more specific symptoms per patient. However a matter of greater interest in this connection is those infants in Group I whose delivery was uncomplicated, in that their average number of symptoms is similar to that of the children in Group IV regardless of the course of delivery.

It is evident—though allowance must be made for the small size of the

frequency following normal and complicated delivery. In infants whose brains were abnormal the average number of symptoms, including the specific ones was slightly higher following complicated than following normal delivery. But one can hardly attach practical importance to these differences.

Parity and maternal age at delivery

132 of the mothers—or 48 per cent—were primiparas. 18 were more than 30 years old, as were 34 of the 143 multiparas. The incidence of primiparity in Copenhagen in 1955 was 37 per cent (Kærn 1955).

The incidence of complications of pregnancy and delivery in the respective parity- and age-groups can be seen from Tables 40 and 41. In elderly multiparas the frequency of pregnancy complications was slightly higher than in the other groups; in elderly primiparas complicated deliveries were somewhat more frequent.

TABLE 40

Complications of pregnancy correlated with parity and maternal age

	Total no.	No. with compl.	Per cent with compl.
Primiparas < 30 years	114	12	11
Primiparas > 30 years	18	1	6
Multiparas < 30 years	109	12	11
Multiparas > 30 years	34	8	24

TABLE 41

Complications of delivery correlated with parity and maternal age

	Total no.	No. with compl.	Per cent with compl.
Primiparas < 30 years	114	52	46
Primiparas > 30 years	18	11	61
Multiparas < 30 years	109	43	39
Multiparas > 30 years	34	15	44

In children of younger mothers asphyxia was commoner following complicated than following normal births, but showed no evident relationship to parity (see Table 42). In children of elderly primiparas (small figures only) asphyxia was common regardless of the course of delivery. However as in the case of younger mothers, it was more frequent following complicated than following normal birth, when the mother was an older multipara. Prolonged asphyxia was evenly distributed throughout the groups.

TABLE 38

A comparison between average number of neonatal symptoms in full-term patients developing severe cerebral sequelae (I) and children developing normally (IV), correlated with conditions during pregnancy and delivery and the presence or absence of asphyxia.

	No. pat. group		Average no. per patient of specific symptoms			
	I	IV	I	IV	I	IV
Pregn. normal, deliv. normal - asphyxia	2	20	2.5	2.1	2.5	0.8
Pregn. normal, deliv. normal + asphyxia	4	9	2.8	2.3	1.5	0.9
Pregn. complic., deliv. normal - asphyxia	1	1	2.0	3.0	1.0	0.3
Pregn. complic., deliv. normal + asphyxia	0	2	0	2.5	0	1.0
Pregn. normal, deliv. complic. - asphyxia	3	12	4.3	1.9	3.3	0.5
Pregn. normal, deliv. complic. + asphyxia	10	8	4.0	2.0	2.5	0.8
Pregn. complic., deliv. complic. - asphyxia	3	2	4.0	2.5	3.0	0
Pregn. complic., deliv. complic. + asphyxia	2	4	4.0	2.2	3.5	0.5

TABLE 39

Autopsy findings in 122 infants who died in the neonatal period correlated with conditions during pregnancy and delivery

	No. pat.	Pregnancy: norm. Delivery	norm. compl. norm.	norm. compl.	compl. compl.
Pulm. atelectasis, normal brain	20	15	1	4	0
Cerebral oedema, pulmonary atelectasis	19	17	0		0
Cerebral haemorrh. ± oedema, pulmonary atelectasis	61	28	6	26	1
Cerebral haemorrh. ± oedema, normal lungs	22	12	2	7	1
Total	122	72 (59 %)	9 (7 %)	39 (32 %)	2 (2 %)

Among the patients who died during the neonatal period more than half had a history of normal pregnancy and delivery (see Table 39) and well over half of these had intracranial haemorrhage. Following complicated deliveries by far the commonest cause of death was intracranial haemorrhage (85 per cent).

An analysis has been made of the incidence of symptoms in the patients with normal brains who died in the neonatal period following normal or complicated delivery and in patients with pathological brains following normal or complicated delivery.

As already mentioned specific cerebral symptoms were absent in the former cases, and the three non-specific symptoms apparently occurred with equal

Frequency of Maternal Age

Frequency of Maternal Age

Frequency of Maternal Age

Frequency of Maternal Age

Age 15-20 4.1%

Age 20-25 4.1%

Age 25-30 4.1%

Age 30-35 4.1%



a)

b)

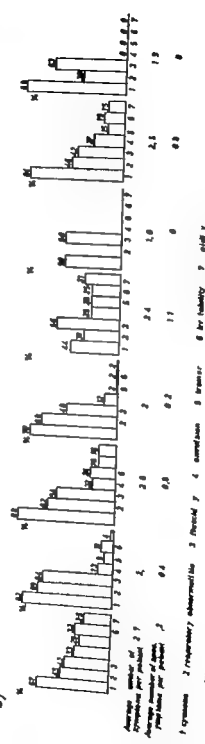


Fig 11 Relationship between maternal age and parity and

) The later condition of the children.
 Minor Patients dying in the neonatal period.
 I-IV Follow-up groups as described in Fig. 9 p. 87
 b) Incidence of neonatal symptoms.

TABLE 42

Frequency of asphyxia in relation to maternal age and parity and course of delivery

Maternal age	Primiparas				Multiparas			
	No deliv. - asph.	comp. + asph.	+ deliv. - asph.	comp. + asph.	N deliv. - asph.	comp. + asph.	+ deliv. - asph.	comp. + asph.
< 30 years	42	20 (32 %)	29	23 (44 %)	30	16 (24 %)	24	19 (44 %)
> 30 years	4	3	6	5	16	3	7	8

In Fig. 11 maternal age and parity are correlated with the severity of late sequelae and the incidence of neonatal symptoms

The mortality rates were almost equal in full-term children of primi- and multiparas under 30 years (well over 30 per cent) and higher than in children of elderly mothers (well over 15 per cent)

The morbidity was higher among firstborn children and obviously the highest among children of elderly primiparas.

Among children of elderly primi- and multiparas mortality and morbidity were essentially unrelated to the course of delivery

Children of younger primiparas had a higher mortality (44 per cent) following a normal delivery than after a complicated delivery (24 per cent) whereas the morbidity was about the same.

Children of younger multiparas had a somewhat higher mortality rate (44 per cent) following a complicated than a normal delivery (37 per cent) however severe sequelae were seen only after complicated deliveries.

The symptomatology was unrelated to maternal age however firstborn children more often exhibited specific cerebral symptoms than children born to multiparas

Labour stimulating drugs

Information about the use of labour stimulating drugs is incomplete. On 123 out of 275 patients no data were available. In the remainder 35 deliveries are known to have been induced in 75 deliveries already in progress, labour stimulating drugs had been used and 42 had not been stimulated. In a great many cases where stimulation had been applied, information on dosage was inadequate.

Despite these deficiencies it was felt to be of interest to analyze the material with a view to detecting possible prognostic differences within the respective groups, particularly interesting because labour stimulation had been applied in 46 cases where no medical indication was stated. In 13 of these cases labour had been induced, in 33 it had been stimulated

Confronted with questions concerning the prognosis in individual patients it might be said that the prognosis is probably poor in the presence of many (more than three) symptoms including two or three of specifically cerebral origin, which is often the case following a complicated birth, regardless of the course of pregnancy or the presence of asphyxia. An infant born by normal delivery—irrespective of the course of pregnancy or presence of asphyxia—exhibiting two or three neonatal symptoms including one or two specific ones, may be prognostically as badly off (the fewer the specific symptoms, the better) if the same symptoms follow a complicated delivery the prognosis will more often be favourable.

The children of elderly primiparas showed no symptomatological differences from children of younger primiparas, however their long-term prognosis was worse. In firstborn children the long-term prognosis, regardless of the mother's age, was more grave than that of children born to multiparas, however they exhibited on average a somewhat higher number of specifically cerebral symptoms.

Complicated pregnancies were too rare to allow definite conclusions as to their influence on the neonatal symptomatology or the prognosis. It was apparent, though, that complications of pregnancy had no decisive influence on the incidence of delivery complications nor of asphyxia.

Intracranial haemorrhage was found to be a common cause of death in cases of normal pregnancy and delivery, however far more frequent following complicated delivery.

Previous studies on the prognostic significance of perinatal conditions

The influence of perinatal conditions on the long-term prognosis has been discussed in numerous papers and conclusions have differed.

Retrospective studies on patients with cerebral palsy have fairly consistently revealed a high incidence of delivery complications. Thus *Phum* (1956) reported complicated deliveries in 50 per cent of his 87 hemiplegics and 202 quadriplegics, but in only about 2.5 per cent of 91 paraplegics and 14 ataxics. *Barclay* (1956) correspondingly found 46 per cent in 144 patients with cerebral palsy and moreover there was a significantly higher incidence of asphyxia following abnormal than normal deliveries. *Skarvedt* (1958) found delivery complications in 44 per cent of 370 children with cerebral palsy. Also *Drillen et al.* (1962) reported a rate of about 50 per cent in a material of full-term and premature diplegics, over 25 per cent and 33 per cent in comparable control series. *Roba*, (1962) found a percentage of 31 in 198 children with cerebral palsy over some 10 per cent in a large control series.

Table 42 a lists the cases where pregnancy and delivery were normal and labour stimulation is known to have been used. Table 42 b gives the corresponding figures in cases with complicated pregnancy or delivery. It will be seen that in the latter the prognosis was essentially the same whether stimulation had been applied or not. This is in contrast to the uncomplicated cases, where the prognosis is obviously graver following induced labour and somewhat worse following stimulated delivery than with non-stimulated delivery.

TABLE 42 a

Relationship between use and non-use of labour stimulation and later condition in 69 cases with normal pregnancy and delivery

	No. pat.	Neonatal deaths per cent	I	Follow-up group II III per cent		IV
Induced delivery	13	38	23	8	15	15
Stimulated delivery	33	24	3	12	15	46
Not stimulated	23	9	4	22	17	48

TABLE 42 b

Relationship between use and non-use of labour stimulation and later condition in 83 cases with complicated pregnancy and delivery

	No. pat.	Neonatal deaths per cent	I	Follow-up group II III per cent		IV
Induced delivery	22	23	27	0	18	32
Stimulated delivery	42	21	17	17	19	26
Not stimulated	19	26	16	16	5	37

Conclusion

The incidence of complicated deliveries in the present series was found to be twice as high as in a normal population. However in 50 per cent of the cases pregnancy and delivery had been perfectly normal, and approximately two-thirds of these had not presented primary asphyxia.

This latter group did not differ in neonatal symptomatology nor with any degree of certainty in prognosis, from the group of non-asphyxiated patients whose births had been complicated.

In each group the presence of primary asphyxia was found to be associated with a somewhat higher number of symptoms per patient. This excess was largely due to an increase in the number of specific cerebral symptoms. Correspondingly the long-term prognosis was worse following asphyxia of short duration. Prolonged asphyxia on the other hand was associated with a high neonatal mortality.

Confronted with questions concerning the prognosis in individual patients it might be said that the prognosis is probably poor in the presence of many (more than three) symptoms including two or three of specifically cerebral origin, which is often the case following a complicated birth, regardless of the course of pregnancy or the presence of asphyxia. An infant born by normal delivery—irrespective of the course of pregnancy or presence of asphyxia—exhibiting two or three neonatal symptoms including one or two specific ones, may be prognostically as badly off (the fewer the specific symptoms, the better) if the same symptoms follow a complicated delivery the prognosis will more often be favourable.

The children of elderly primiparas showed no symptomatological differences from children of younger primiparas, however their long-term prognosis was worse. In firstborn children the long-term prognosis, regardless of the mother's age, was more grave than that of children born to multiparas, however they exhibited on average a somewhat higher number of specifically cerebral symptoms.

Complicated pregnancies were too rare to allow definite conclusions as to their influence on the neonatal symptomatology or the prognosis. It was apparent, though, that complications of pregnancy had no decisive influence on the incidence of delivery complications nor of asphyxia.

Intracranial haemorrhage was found to be a common cause of death in cases of normal pregnancy and delivery however far more frequent following complicated delivery.

Previous studies on the prognostic significance of perinatal conditions

The influence of perinatal conditions on the long-term prognosis has been discussed in numerous papers and conclusions have differed.

Retrospective studies on patients with cerebral palsy have fairly consistently revealed a high incidence of delivery complications. Thus Plum (1956) reported complicated deliveries in 50 per cent of his 87 hemiplegics and 202 quadriplegics, but in only about 25 per cent of 91 paraplegics and 14 stasics. Barclay (1956) correspondingly found 46 per cent in 144 patients with cerebral palsy and moreover there was a significantly higher incidence of asphyxia following abnormal than normal deliveries. Skarvedt (1958) found delivery complications in 44 per cent of 370 children with cerebral palsy. Also Drillen *et al.* (1962) reported a rate of about 50 per cent in a material of full-term and premature diplegics, over 25 per cent and 33 per cent in comparable control series. Roboz (1962) found a percentage of 31 in 198 children with cerebral palsy over some 10 per cent in a large control series.

Opinions have differed on the role of delivery complications in the aetiology of cerebral palsy. However, it can hardly be doubted that a pathological delivery in certain cases is of primary significance. Several prospective studies have led to the opposite conclusion.

Wetterdal (1951) carried out a follow-up study at age 12 years, on 2000 children delivered spontaneously and 2000 children delivered by forceps, of whom about one-quarter had exhibited perinatal asphyxia. He found a higher neonatal mortality among the latter. By contrast, there were no differences in the incidence of physical or mental handicaps. 75 per cent were perfectly normal. The follow-up percentage was 82–85.

Keith Norval and Huns (1953) concluded that neither prolonged delivery nor asphyxia caused neurological abnormalities in children who survived the neonatal period. This conclusion was based on follow-up examination at the age of 4 years of approximately 400 children whose birth had been prolonged, well over 200 children who had exhibited primary asphyxia, and controls for both groups. Their findings were confirmed at re-examination at the ages of 4 to 14 years (*Keith and Gage* 1960). The follow-up percentage was 76–79. All the groups included children who had exhibited neonatal symptoms: a majority were found in the asphyxia group (23 per cent) almost as many in the groups with prolonged delivery (8 per cent) as in that with normal delivery (4 per cent). Among these infants the neonatal mortality was very high (about 50 per cent) regardless of the course of delivery or of asphyxia, but the children who survived the neonatal period were neurologically normal. The mortality rate in the present material thus is somewhat lower while the late morbidity is much higher. This may be ascribed to differences in selection. Keith and Norval's series came from an obstetric department and is apt to include more cases of neonatal deaths. The current material is composed of children who had survived the first few hours or days of life, however exhibited symptoms severe enough to prompt their transfer from the place of delivery to a paediatric department. At follow-up those children from Keith and Norval's series who exhibited no neonatal symptoms but asphyxia were neurologically normal whereas in the groups with prolonged delivery and with normal delivery 4–5 per cent showed neurological deviations such as mental retardation, epilepsy, febrile convulsion and squint. The defects were evenly distributed throughout the groups.

Benaron et al. (1953) correspondingly found similar prognoses in children surviving the neonatal period following prolonged labour plus forceps delivery even when associated with prolonged primary asphyxia, and following a normal delivery. Precipitate deliveries, however, were apt to leave residua. Each group consisted of well over 40 children, who were re-examined at the ages of 5–15 years.

Kramer and Nack (1957) carried out a follow-up study on 75 of 214 children delivered by forceps and 75 children born spontaneously and found no differences in mental development, nor did they find any neurological defects in any of the groups.

Primary asphyxia has been the subject of numerous studies. Its frequency is fairly constant in unselected obstetric materials. Russ, Strong and Christian (1946) thus found rates of 2 to 3 per cent, Campbell Cheeseman and Kilpatrick (1950) had 4.4 per cent in well over 6000 births, Benaron *et al* (1960) 6 per cent in some 40 000 births, and Häler (1962) 2.2 per cent in about 9 000 cases—all much lower than the incidence found in the present series (35 per cent).

As regards the influence of asphyxia on the later development of a child conclusions differ widely which to some extent may be explained by differences in the methods of selection as well as in the definition of asphyxia.

Several authors considered asphyxia as unimportant. McPhall and Hall (1941) collected precise data on the course of delivery and immediate post-natal condition in 1005 infants. 8.9 per cent had mild asphyxia (apnoea for less than one minute), 6 per cent had severe asphyxia (apnoea for more than one minute or cyanosis during the first few days of life), 0.7 per cent were stillborn, 1.1 per cent died during the neonatal period and 83.3 per cent had not exhibited asphyxia.—Mild asphyxia was found to be slightly commoner following prolonged deliveries. However a marked predominance of severe asphyxia was evident in cases with precipitate labour, forceps deliveries and breech presentations. Mainly for geographical reasons only 270 children were re-examined at school-age. (The ratio of asphyxiated/non-asphyxiated cases was about the same as in the original series.) No mental or behavioural differences were demonstrated in any group.

Similar findings were reported by Campbell Cheeseman and Kilpatrick (1950) on follow-up at ages 8–11½ years of children who had exhibited fairly severe asphyxia, viz. asphyxia pallida or asphyxia livida for more than two minutes. A greater number of asphyxiated than non-asphyxiated children had a history of complicated birth. The material consisted of 267 children, 178 of whom had not exhibited asphyxia. The follow-up rate was 73 per cent.

Uchls and Weis (1952) compared at the age of 13–14 years a group of full-term children who had exhibited neonatal asphyxia for more than three minutes, but were otherwise without cerebral features, with a matched control series. They found no difference in mental development between the two groups. The original material consisted of 180 patients, but the follow-up percentage was less than 50.

Similarly Uchls (1965) found no difference in intellectual or emotional development between asphyxiated and non-asphyxiated children. On the

other hand, he found that the former were apt to exhibit marked sensitivity violent reactions and failure to adjust to new situations. Ucko's material consisted of 29 children who were neurologically normal, but had suffered varying degrees of asphyxia in the neonatal period, and 29 non-asphyxiated children. Their ages were up to five years at follow up

Other writers have found minor but still definite sequelae. *Fraser and Wilks* (1959) thus reported slight retardation of motor development and a possible perceptual disturbance (figure-background perception) but extensive investigations revealed no additional deviations. They had studied 100 asphyxiated children, of whom 40 had suffered severe asphyxia (i. e. for more than 5 minutes a majority for 15 minutes or more) All were born at term. Children who had presented cerebral symptoms in the neonatal period had not been excluded from the material. Comparable controls were also examined. The age at follow up ranged from 7 to 11 years.

Walker (1964) found a tendency—though not of statistical significance—towards poorer performance, intellectually as well as physically in premature children who had suffered asphyxia neonatally compared with a group of non asphyxiated premature children and a group of non asphyxiated mature children. The age at follow up was 10 to 12 years. There were 41 children in each group

Stechler (1964) followed-up 26 full term firstborn children, of whom 9 had been asphyxiated for 2½ to 16 minutes and found in the asphyxiated a significantly slower development up to the age of 2 years. Thereafter their development was normal except for a somewhat more uneven performance between one test and the next.

Other writers found more definite correlation. *Darke* (1944) stated that 19 severely asphyxiated children showed significant mental retardation compared with a control series. The criteria for selection were asphyxia pallida or asphyxia exceeding three minutes in the absence of neurological symptoms during the neonatal period as well as later

Benaron et al (1960) also reported a higher incidence of mental retardation (20 per cent) among 30 children who had sustained severe neonatal asphyxia persisting for not less than 10 minutes to more than an hour compared with 54 controls (2.5 per cent). The average IQ score, on the other hand, was equal in the two groups, indicating a greater spread among the asphyxiated. The latter moreover had a higher rate of EEG-abnormalities and persistence of infantile habits. There were, however, no developmental or neurological differences. About 70 per cent of the children were re-examined at the age of 10 years.

Ernhart Graham and Thurston (1958) and *Graham Ernhart and Thurston* (1962) found that children who had sustained perinatal anoxia, particularly post-natal, often showed a poor intellectual performance and also ex

hibited more neurological defects at the age of three years than children who were neonatally normal. The series consisted of 116 full-term anoxic children, of whom 36 had showed evidence of possible intrauterine anoxia, 42 of postnatal anoxia of varying degree (apnoea persisting for less than one minute to over 4 minutes or secondary apnoea only) and 38 of prenatal as well as postnatal anoxia. None had exhibited other cerebral features. The control series consisted of 159 mature children. The follow-up rate was about 85 per cent.

In another investigation *Graham Ernhart, Thurston and Craft* (1962) studied a small group of children who had presented clinical evidence of birth injury during the neonatal period. At the age of three years they differed from a normal group only in terms of a significantly higher incidence of neurological defects.

Hüter (1962) over a three-year period gathered 201 full-term infants exhibiting asphyxia of varying degree (apnoea ranging from less than one minute to over four minutes, associated with varying changes of muscle tone) 27 children, who had been severely asphyxiated, died within the neonatal period, their neonatal condition, however, was not described. 104 (about 50 per cent) were re-examined at the age of 2 to 5 years. The incidence of sequelae was very high. 27 per cent had cerebral palsy of varying degree, well over one half were also mentally retarded, as were 21 per cent who were neurologically normal. A positive correlation between the degree of cerebral damage and that of asphyxia was demonstrated. Similarly a positive correlation was established between the degree of asphyxia and conditions during pregnancy and delivery predisposing to hypoxia, however information about these conditions was only available in the cases exhibiting sequelae.

No clearcut conclusion can be drawn from this diversified picture. Conditions surrounding delivery are so complex that this could hardly be expected. The course of the delivery is not all-important; however it seems to be universally agreed that complicated deliveries are more often associated with asphyxia, and this is also demonstrated in the present material.

In most cases *Dekaban's* statement (1959) will probably be true: the prognosis for life is grave in the presence of asphyxia pallida, though not in the milder forms of asphyxia. On the other hand, these are more often associated with late cerebral defects. The very mild forms apparently have no bearing on the later course. Yet even very prolonged asphyxia is compatible with later normal development. The uncertainty in establishing the prognosis is probably due to the difficulties in determining the origin of asphyxia, which may also play a decisive role. Neonatal symptoms seem to offer a more reliable prognostic indication than either the course of delivery or asphyxia.

CHAPTER VII

Prematurity

As previously mentioned 35 per cent of the children in the present material were premature (The prematurity rate in Copenhagen in 1948 was 7 per cent) For practical reasons the premature patients have been treated so far as one group which obviously is incorrect. In Table 43 the group has been subdivided according to BW and compared with the mature children.

As might be expected the mortality rate is higher the lower the BW Only two patients in the weight group of 1500-1000 grams survived the neonatal period. The one infant weighing less than 1000 gm died.

Otherwise it should be noted that the later progress of the premature survivors was as good as, if not better than the mature.

The premature infants, as previously stressed, exhibited on average fewer symptoms than the mature. This appeared to be more pronounced as the BW decreased. The number of symptoms per patient among premature survivors was, in the order of decreasing BW 2, 1 2, 1 and among those who died within the neonatal period. 2 9 2.5 2 1 and 2.

It should be noted, too that the rate of prematurity varied with maternal age. in mothers under 30 years it was 39 per cent among primiparas and 38 per cent among multiparas, while the corresponding rates in older mothers were 11 and 24 per cent, respectively

TABLE 43
Relationship of BW to mortality and results at follow-up

Birth weight in grams	No.	Neonatal deaths no.	Mortality rate per cent	No. of survivors	I	Follow-up group II per cent	III	IV
> 2500	179	55	31	124	20	15	18	47
2000-2500	39	21	53	18	11	17	17	55
1500-2000	35	26	74	9	22	-	56	22
1000-1500	21	19	90		-	100	-	-
< 1000	1	1	100	0				
< 2500	96	67	70	29	14	17	28	41

Complications of pregnancy were slightly more common prior to premature deliveries (13 per cent) than prior to deliveries at term (9 per cent) while complications of delivery were commoner at term (50 per cent) than before term (32 per cent)

Previous studies on the prognosis in premature infants

In view of the great difficulties of neonatal diagnostics in premature infants it was considered of special interest to compare the present study with a selection of the numerous investigations into the later progress of premature children. The following section includes only prospective studies. It may be mentioned, however that the prematurity rate in retrospective analyses of patients with cerebral palsy has been found to be uniformly high, ranging from 17 to 39 per cent (A. o. *Asher and Schonell* 1950 *Denhoff and Holden* 1951 *Barclay* 1956 *Plum* 1956, *Fuldner* 1957 and *Skarvedt* 1958)

But a few of the studies are immediately comparable. Some originate in obstetric clinics, others in paediatric departments. Consequently there may be differences in the composition of the materials due to differences in criteria for admission. Moreover the percentage of complicated deliveries varies at different obstetric clinics. Some series are unselected, others exclude patients with neonatal complications; still others disregard patients without neonatal complications. Some include twins. Some apply a social selection. Moreover the upper limit of birth weights varies, some writers have included all infants below 2500 grams, while others incorporate only infants weighing less than 2000 or 1500 grams. Finally the follow-up rates vary considerably

Table 44 gives a survey of the results of previous studies, but considers severe sequelae only

It is apparent that the frequency of handicaps generally is higher amongst infants with a lower BW (cerebral palsy in 0.4–8.3 per cent with BWs up to 2500 gm, and 7–40 per cent below 1500 gm, the total incidence of severe handicaps being 5–20 per cent and 7–53 per cent, respectively)

This relationship has been particularly stressed by *Ylppö* (1919) and *Knobloch, Rider Harper and Pasamanick* (1956) Moreover several authors have found the average IQ of premature children to be obviously lower than in a comparable group of mature children (see among others *Ylppö* 1919 *Sande* 1930 *Alm* 1953 *Blegen* 1953 *Drillien* 1959 and 1961 *Dann* 1958 and 1964 *Frisk* 1964 *Marstrand* 1964 and *Wohlmut and Frater* 1965) Likewise the growth rate of the premature has been described as retarded by almost all workers, at least during the first years of life, and particularly in small prematures (all the authors mentioned above plus *Illingworth* 1939 and *Lubchenko et al.* 1963)

Author	Year	Number	BW	Selection	Neonatal mortality %
Ylppö	1919				
Comberg	1927	233	≤ 500 g	high soc. (pard.)	58 (1 yr)
Capper	1928	437	≤ 2000 g	0 (pard.)	44 (1 yr)
Sunde	1930	1423	≤ 2500 g	0 (ob.)	36 (1 yr)
Friedländer	1934	178	≤ 2500 g	0 (pard.)	37 (1 yr)
Ilmgworth	1939	150	≤ 2500 g	0 (pard.)	
Beakow	1949	289	≤ 2500 g	incl. 6 % neonatal sympt. (pard.)	
Blegen	1953	1127	≤ 2500 g	0 (ob.)	15.5
Knobloch et al.	1956	500	< 2500 g	pard. - gemelli	
		492	> 2500 g		
Harper et al.	1959	460	< 2500 g	pard. - gemelli	
		440	> 2500 g		
Drillien	1959	165	< 500 g	0 (pard.)	
		427	> 2500 g	0 (pard.)	
Frisk et al.	1964	94	≤ 1750 g	0 (pard.)	32
Helmer et al.	1964	444	≤ 2100 g	{ - gemelli, - cong. anomaly - bloodtype incompat. (pard.)	
Mc Donald	1963	1128	≤ 1800 g	0 (pard.)	
Marstrand	1964	80	< 2000 g ($> 1 < 1500$ g)	0 (pard.)	-
				14 abn. neonatal all sympt. neonatal (pard.)	
Hess et al.	1934	69	≤ 500 g	all sympt. neonatal (pard.)	
Hess	1953	88	< 1250 g	all sympt. neonatal (pard.)	
	-	1593	< 1250 g	pard.	72
Drillien	1959	92	< 1360 g	0 (pard.)	-
	1961	50	< 1360 g	0 (pard.)	
Dann et al.	1958	116	< 1280 g	0 (pard.)	
Roesler	1962	175	< 1500 g	0 (pard.)	
Lubchenco et al.	1963	187	< 1500 g	0 (pard.)	47
Silagay et al.	1965	112	≤ 2500 g	susp. i. c. h. neonatal	
Wohlmuth et al.	1965	284	≤ 2500 g	0 (pard.)	22

) 47 % of total material and 57 % of followed-up patients suspected of her haem. neonatal

H
 the prognosis of premature children

Follow-up rate of survivors %	Age at follow-up years	Major sequelae	Total nos.
		3.1 % c. p. + 7.4 % mental defic.	10.5 %
81	3-7	2 % c. p., 3 % mental defic.	5 %
84	14	5 % c. p. + 7 % ment. defic. + 3 % epilepsy	17 %
82	6-21	7 % defic., incl. 5.7 % mental defic.	7 %
88	5-10	0 c. p., 19 % varying degree, mental defic.	19 %
	pre-school + schoolage	20 % c. p. + mental defic. + epilepsy	20 %
90	9-13	3.1 % c. p., 2.4 % debil. ment.	5.5 %
79	10-18	0.4 % c. p., 4.6 % mental defic., 7.5 % debil. ment.	12.5 %
91	40 weeks	BW \leq 1500: 26 % neurol., 11.6 % mental defic. all BWs < 2500: 8.3 % neurol., 1.9 % mental defic. BW > 2500: 1.6 % neurol., 1.2 % mental defic.	38 % 10 % 2.8 %
77	3-8	BW \leq 1500: 20.4 % neurol. handicaps all BWs < 2500: 4.1 % neurol. handicaps BW > 2500: 2.3 % neurol. handicaps	
	2	3 % c. p.	
	2	0.5 % c. p.	
84	6-7	40 % c. p.	
71		19.7 % neurol. abn.	19.7 %
96	6-8	6.5 % c. p.	
100	18 mo.		22 %
		40 % c. p., mental defic.	40 %
		33 % c. p., 13.7 % mental defic.	46 %
83	1 III	15 % phys. handicap, 11 % mental defic.	
	2 10	22 % neurol. handicaps, 14 % mental defic.	27 %
	acc. 9	12 % c. p., total 53 % phys. handic., 30 % ineducable norm. schools	
88	born 1940-52 acc: 1950-57	6.8 % c. p., epil., hearing loss	6.8 %
91	4-7	7 % c. p., 11.5 % mental defic.	
65	10	35 % c. p., 25 % mental defic.	
80	1-7	26 % mental defic. \pm c. p. \pm epil.	26 %
68	4-7	3 % c. p. + 3 % sensory defect + 47 % minor motor + mental	53 %

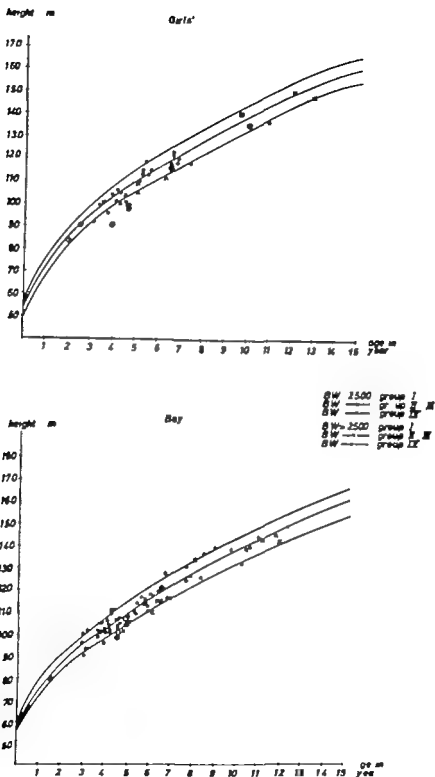


Fig 12

Height in centimetres at follow-up of 85 girls and 45 boys.
(Normal records according to A. Sandal, Nord. Lærebog i Pædiatri 1967).

Numerous hypotheses have been suggested as to the causes of these handicaps, a subject which, however, is not under discussion in this book. It may be mentioned though that among others *Ylppö* (1919) *Comberg* (1927) *Hess* (1934), *Beskow* (1949), *Alm* (1953) and *Wohlmuth and Frater* (1965) advocate the theory of intracranial injury rather than prematurity itself as the causative factor. This theory is supported by the fact that in the series dealing exclusively with premature children with neonatal symptoms suggesting intracranial damage there is a conspicuously higher incidence of sequelae (26-53 per cent) than in unselected materials. This is demonstrated among others by *Hess* (1934) *Beskow* (1949) *Silagy* (1965) (*Wohlmuth and Frater* (1965) and also by the present author (31 per cent in Groups I and II).

In the small premature, however, the rate of handicap is equally high whether the material is unselected or not. This may be explained by the fact that a large number of cases of cerebral damage in this weight group are almost entirely asymptomatic. This is at variance with *Drillen* (1959) who reported more neonatal cerebral symptoms in the weight group below 1500 grams than in a mature group. Nonetheless, the incidence of handicaps among the small premature remained unchanged regardless of the neonatal course.

The height has been measured in 130 of the 153 patients in the present series (26 premature and 104 mature). A total of 27 patients measured below lower normal borderline limits (see Fig. 12). Of these 7 were premature and 20 were mature, i.e. the premature (about one-quarter) outnumber the mature (about one-fifth) to only a small degree. It must be considered, though, that only two infants in the premature group had BWs below 1500 grams (both were of normal height). On the other hand there is a proportionally greater difference in the incidence of low height between Group I (8 out of 18) and the other groups (19 out of 112, evenly distributed in groups II, III and IV). This suggests that cerebral damage rather than prematurity in itself determines this aspect also.

CHAPTER VIII

Sex differences

In the total material boys (63 per cent) outnumbered girls (the ratio between boys and girls born alive during the same period was approximately 52 over 48 per cent). As shown in Table 45 no prognostic differences between the sexes were demonstrable.

The rate of prematurity was somewhat higher in the girls (40 per cent) than in the boys (32 per cent) but mortality rate and long-term prognosis were equal within all weight groups.

One difference was found in the infants who died during the neonatal period, there was a significantly higher incidence of cerebral oedema in the boys (see Table 46). No explanation can be offered for this finding. As previously mentioned, the original series had been enlarged by 41 patients who died of cerebral oedema during the neonatal period. Also in this group there was a predominance of boys over girls (27 and 14 respectively).

TABLE 45
Mortality and prognosis related to sex

	Neonatal mortality per cent	No. of survivors	I	Follow-up group II per cent III IV		
Girls 103 (37 per cent)	43	59	19	10	20	51
Boys 172 (63 per cent)	45	94	19	19	19	43

TABLE 46
Autopsy findings in 122 neonatal deaths related to sex

Autopsy findings	44 girls	78 boys
Pulmonary atelectasis, normal brain	10 (23 %)	10 (13 %)
Pulmonary atelectasis, cerebral oedema	2 (4 %)	17 (22 %)
Pulmonary atelectasis, cerebral haemorrhage \pm oedema	24 (55 %)	37 (47 %)
Cerebral haemorrhage \pm oedema, normal lungs	8 (18 %)	14 (18 %)
All patients with cerebral oedema	11 (25 %)	36 (46 %)

Summary

The object of the present study was the evaluation of the specificity of presumed cerebral symptoms and the prognostic value of neonatal symptoms.

Chapter I presents a review of previous literature on cerebral symptoms in newborn infants with special regard to studies comparing clinical and pathological findings. It is stressed that the clinical diagnosis of cerebral damage in the newborn is difficult, since the presenting symptoms are often non-specific and in many cases few in number. The commonest symptoms were cyanosis, respiratory irregularities, changes in consciousness and tone, convulsion and failure to suck. None of these, however, have been found to be specifically cerebral.

In addition, previous studies on the prognosis of intracranial neonatal disorders are reviewed. The materials are difficult to compare, primarily due to differences in the criteria of selection, but also because of great variations in the follow-up rates and in the age of the children at follow-up. In spite of these dissimilarities the incidence of severe cerebral sequelae varied as little as 10 to 30 per cent. However, opinions differ considerably as to what clinical symptoms may be of the greatest prognostic significance. No definite conclusion was possible.

Finally mention is made of some recent methods of investigation stressing the importance of the neurological examination during the neonatal period. The prognostic value of these studies can be judged only when long-term examinations have been completed.

Chapter II describes the present material, which includes 291 children who had been admitted to the Department of Paediatrics at Copenhagen County Hospital at Gentofte during the neonatal period. The data were obtained from the records, which had been selected on the basis of diagnoses that either 1) suggested cerebral damage: intracranial haemorrhage, sequelae of difficult delivery, fracture of the skull, asphyxia neonatorum, or 2) suggested the presence of some of the symptoms exhibited by the former group, such as pulmonary atelectasis, aspiration into the lungs, congenital debility. Patients who might have presented similar symptoms, but were re-

gistered under other definite diagnoses such as proven heart disease or hiatus hernia have been disregarded. Patients with severe neonatal jaundice were also excluded. In addition to neonatal symptoms and clinical course during admission all available information on pregnancy and delivery was recorded.

Most frequent among the neonatal symptoms was cyanosis, which occurred in three-quarters of the patients. Respiratory disturbances and flaccidity were observed in well over one half, convulsions in almost one-quarter and tremor irritability and rigidity in about one-fifth of the cases. A wide variety of combinations of these symptoms was recorded. The average number of symptoms per patient was 2.5. Among the premature patients, representing 35 per cent of the series, the rate was somewhat lower (2.3) than among the mature (2.7). Convulsion, tremor irritability and rigidity were relatively rarer in the premature.

The patients were born in the period from 1946 to 1955 inclusive. The follow up examinations were performed from 1958 to 1959. Sixteen children had to be excluded owing to lack of information about their later development. Twelve had died after discharge from the hospital, but are nevertheless included in the material, since sufficient data on the subsequent course, in some instances detailed autopsy reports, were available. In six cases information derived only from written reports from the parents and/or their private doctor. The remainder have been examined by the author. The follow up rate is 95 per cent.

The follow-up included a general physical and neurological examination as well as an evaluation of the mental condition of the children. A meticulous history was taken, with special weight being given to mental, motor and somatic development. Moreover reports were obtained from specialists who, in some cases, had been consulted prior to the follow-up (psychological testing, eye and ear examinations, speech evaluation and electroencephalography). In a few instances, where it was thought to be indicated, and when practically possible, the children had been referred for such examinations in the course of the follow-up.

In the description of *the results at follow-up* the cases have been divided into those dying during the neonatal period and four groups of survivors.

122, or 44 per cent of the patients died during the neonatal period. Macroscopic autopsy reports were available in all these cases, and the assessed causes of death as well as additional abnormal findings are described. In 84 per cent the primary cause of death was intracranial haemorrhage or cerebral oedema, or a combination thereof. In 16 per cent there were no abnormal changes in the brain the cause of death being pulmonary atelectasis.

29 or 11 per cent (or 19 per cent of the survivors) had severe cerebral sequelae. 18 patients were mentally defective and exhibited severe neurolog-

ical symptoms, 7 had mental and motor handicaps of varying degree and 4 showed neurological symptoms, but had normal intelligence. 12 of the mentally retarded patients had died, the majority at the age of 2 to 3 years. Convulsion occurred in 16 speech retardation in 21 impaired hearing in at least 5 and squint in 15 patients. A description is given of EEGs in 21 cases, of pneumoencephalograms in 13 of brain sections in 7 and of head circumference in 20. Evidence of cerebral atrophy was found in 21 of these 29 patients.

24, or 9 per cent (or 16 per cent of the patients who survived the neonatal period) had minor cerebral sequelae in the form of mild mental retardation, temporary retardation of motor development or growth, recurrent convulsions—febrile or afebrile—hearing defects, aphasia or retardation of speech, temporary hyperactivity during the first one or two years of life, behaviour disorder squint and emmetropia. All the children exhibited more than one of these features in varying combinations. None had permanent motor handicap.

30, or 11 per cent (or 19 per cent of the survivors) had mild, presumably cerebral deviations of similar kind, however less pronounced than in the previous group, and most of the children exhibited a single symptom only. In this group there were also five cases of dyslexia, but none of mental retardation, afebrile convulsion or hearing loss.

70, or 25 per cent (or 46 per cent of the survivors) presented no abnormal features.

The possible relationship between the abnormalities found at follow-up and the neonatal condition is discussed with reference to the literature. Adequate support is felt to have been forthcoming as far as later severe cerebral sequelae are concerned, but also for the milder symptoms, to maintain the assumption of a neonatal origin with reasonable certainty.

In *Chapter III* the diagnostic significance of the neonatal symptoms is evaluated by comparing the features observed in patients dying during the neonatal period from 1) pulmonary atelectasis (associated with normal brain) (20 patients) 2) pulmonary atelectasis and cerebral oedema (19 patients) 3) pulmonary atelectasis and intracranial haemorrhage \pm cerebral oedema (61 patients) and 4) intracranial haemorrhage \pm cerebral oedema (normal lungs) (22 patients).

The symptoms of convulsion, tremor irritability and rigidity were found exclusively in patients with pathological brains. With a view to corroborating this observation the material has been expanded to include an additional 26 patients dying during the neonatal period of pulmonary atelectasis. None of these exhibited any of the aforesaid symptoms.

Although these symptoms thus seemed to be specifically cerebral, their absence by no means excludes the diagnosis of intracranial haemorrhage.

gistered under other definite diagnoses such as proven heart disease or hiatus hernia, have been disregarded. Patients with severe neonatal jaundice were also excluded. In addition to neonatal symptoms and clinical course during admission all available information on pregnancy and delivery was recorded.

Most frequent among the neonatal symptoms was cyanosis, which occurred in three-quarters of the patients. Respiratory disturbances and flaccidity were observed in well over one half, convulsions in almost one-quarter and tremor, irritability and rigidity in about one-fifth of the cases. A wide variety of combinations of these symptoms was recorded. The average number of symptoms per patient was 2.5. Among the premature patients, representing 35 per cent of the series, the rate was somewhat lower (2.3) than among the mature (2.7). Convulsion, tremor, irritability and rigidity were relatively rarer in the premature.

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In Chapter V the neonatal symptoms are evaluated in relation to the long-term prognosis by comparing their incidence in the four follow-up groups of survivors (I. 29 patients with severe cerebral sequelae, II. 24 patients with minor cerebral sequelae, III. 30 patients with mild, presumably cerebral deviations, and IV. 70 children with no abnormal findings at follow-up).

The average number of symptoms per patient is found, in the mature, to be the highest in Group I (3.6 over 2.1 in Group IV). Moreover there was a clear predominance of specific symptoms in Group I with 92 per cent having one or more such features over about 40 per cent of the mature children in the remaining groups and about 25 per cent among the premature in all groups.

An evaluation of the prognostic significance of each symptom and combination of symptoms in the full-term infants gave the following results. In the presence of a single symptom—whether specific or non-specific—the prognosis was relatively good, with a less than 10 per cent risk of severe cerebral sequelae and a 50 per cent chance of a perfectly normal development (75 per cent, if including Group III with dubious sequelae). The rates were essentially similar in the presence of two neonatal symptoms, even including one specific, and in the presence of three non-specific symptoms. When two specific symptoms were combined, the outlook appeared to be worse, with about a 30 per cent risk of severe cerebral sequelae. With an increasing number of symptoms, especially specific symptoms, the prognosis worsened. With a combination of not less than three symptoms, at least one being specific, there was a 40–60 per cent risk of severe sequelae and as high as 60–80 per cent, if no less than two of the symptoms were specific.

Cyanotic attacks—in association with other symptoms—when beginning during the first day of life and persisting beyond the fourth day were a grave prognostic sign. Delayed cyanotic attacks were prognostically unfavourable if persisting for more than 2 days, while attacks limited to one day had no serious implications.

Convulsions appeared to imply a fairly grave outlook, even when limited to one or two days, more so when persisting for more than three days.

In the premature the evaluation was somewhat difficult because so few patients survived the neonatal period, and partly because the premature mostly exhibited very few symptoms, in particular very few specific symptoms. It was found, however, that as many as three symptoms, even when one or two were specific, did not always imply a grave prognosis.

The role of aetiological factors as related to the diagnostic and prognostic

or cerebral oedema. 46 per cent of the mature infants and as many as 79 per cent of the premature whose brains were found to be abnormal at autopsy exhibited only cyanosis, respiratory abnormalities or flaccidity i.e. the features observed in patients who died from pulmonary atelectasis. The differential diagnosis between these groups is thus very difficult.

Permanent cyanosis was somewhat commoner among the infants with pulmonary atelectasis on its own while cyanotic attacks were more frequent among those with abnormal brain however both forms of cyanosis were too common in each group to allow diagnostic conclusions. In contrast, delayed cyanotic attacks (onset on the second or third day of life) were noted in brain-damaged infants only.

The study revealed no clinical differences between cases of cerebral oedema and of intracranial haemorrhage. All the symptoms occurred with equal frequency in each group. Neither was there any difference in the incidence of permanent or attackwise cyanosis nor in the time of onset of cyanosis. This also applied to time of onset and duration of convulsions.

The addition to the material of 41 patients dying of cerebral oedema during the neonatal period did not change these observations.

The significance of the neonatal symptoms for the prognosis for immediate survival is discussed in *Chapter IV*. The infants who died during the neonatal period exhibited on average more symptoms than those who survived, and it is inferred that with an increased number of symptoms the risk for life is greater. This was true in the mature patients, among whom the average number of symptoms was 3.1 against 2.5 in the survivors, as well as in the premature, where the corresponding figures were 2.5 and 1.7. However death did occur in the neonatal period, in a number of patients, mature as well as premature, who exhibited a single symptom only.

The mortality rate has been calculated for each neonatal symptom occurring alone (which was rare) as well as in association with other symptoms. Cyanotic attacks within the first 24 hours of life, difficult and grunting respiration, hypotonicity and convulsion were found to imply a grave prognosis in the premature, the mortality rate being about 80 per cent, while in the mature it was only about 40 per cent. In mature infants cyanotic attacks beginning later than the first day were found to be a more unfavourable prognostic sign than cyanotic attacks occurring during the first day (mortality rate 56 against 27 per cent). Cyanotic attacks were commoner than permanent cyanosis (77 per cent over 23). The latter when persisting beyond a few hours, as in periodic apnoea, were invariably fatal as might be expected.

The more specifically cerebral symptoms convulsion, tremor irritability and rigidity seemed to indicate a less serious immediate prognosis in the mature (mortality rate 20-30 per cent) than the non specific symptoms.

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The role of aetiological factors as related to the diagnostic and prognostic

value of the neonatal symptoms is the main subject of *Chapter VI* which deals with conditions during pregnancy and delivery as well as with the occurrence of asphyxia. Asphyxia here is defined as delayed initiation of spontaneous breathing following birth.

Complications of pregnancy were reported in 12 per cent of the mothers and was thus too rare to allow conclusions as to their significance. It was, however evident that complications of pregnancy had no decisive influence on the frequency of complications of delivery nor of asphyxia.

Complications of delivery occurred in 44 per cent of the cases, or twice as often as in a normal population.

35 per cent of the children had been asphyxiated. (The incidence of asphyxia in unselected obstetric series is found to be 2-6 per cent) In the present material asphyxia occurred twice as often following a complicated delivery as following a normal delivery

In 50 per cent of the cases pregnancy and delivery were normal, and in two-thirds of these the infants did not exhibit asphyxia. The neonatal symptomatology of this group did not differ from that of the group of non-asphyxiated infants whose birth was complicated, nor did their prognosis differ with any certainty

In the presence of asphyxia, following normal as well as complicated deliveries, there was a slight increase in the number of neonatal symptoms, mainly of those specifically cerebral in origin. This was paralleled by a graver prognosis following asphyxia of short duration. Asphyxia, when persisting for more than five minutes, was associated with a high neonatal mortality rate.

The course of the delivery apparently had some bearing on the prognostic value of the neonatal symptoms in so far as a child whose birth was normal, who exhibited two or three neonatal symptoms including one or two specific symptoms, more often would have an unfavourable prognosis than a patient with the same combination of symptoms following a complicated delivery. This was true regardless of the course of pregnancy or of the occurrence of asphyxia.

In 72 of the 122 fatal cases both pregnancy and delivery had been uncomplicated. In 55 per cent autopsy disclosed intracranial haemorrhage. In 41 fatal cases the delivery had been complicated 85 per cent of these had intracranial haemorrhage. No symptomatological differences were demonstrable.

Firstborn infants were found on average to have slightly more specific symptoms than children of multiparas, and this was paralleled by a higher incidence of sequelae. Children of elderly primiparas did not differ symptomatologically from children of younger primiparas however they had a less favourable long-term prognosis.

The available data on the administration of labour stimulating drugs was scanty and has been only briefly mentioned. It was noted that children born by induced or stimulated deliveries, the course of pregnancy and delivery being otherwise normal, seemed to do less well than children born by non-stimulated normal deliveries.

Previous studies on the prognostic significance of the perinatal condition are reviewed. Opinions have varied considerably as to the influence of birth injury and asphyxia. However, these divergencies may be explained to a large extent by differences in the selection of materials. The course of delivery though not all-important, seems in certain cases to be of primary importance for the development of later cerebral defects. Asphyxia is commoner following complicated deliveries than following normal deliveries. In severe cases it is often associated with neonatal death in milder cases cerebral sequelae are quite frequent. However the neonatal symptoms seem to give more reliable indications for the prognosis than the course of delivery and asphyxia.

Chapter VII deals with aspects of prematurity. The rate of prematurity was very high (35 per cent over about 7 per cent in a normal population) and the neonatal mortality rate was considerably higher (70 per cent) than among the mature patients (31 per cent) the lower the birth weight, the higher the mortality.

On the other hand no late-prognostic differences were demonstrated between premature and mature children. (31 per cent of the former and 35 of the latter had severe or minor cerebral sequelae)

Symptomatically the premature differed from the mature in exhibiting fewer neonatal symptoms. This was more pronounced the lower the birth weight.

A review is given of previous studies on the prognosis of premature children. The materials, however are not directly comparable owing to varying criteria of selection and varying follow-up rates. It is evident, though, that among premature children with very low birth weights, or presenting neonatal cerebral symptoms, there was a higher percentage of cerebral sequelae than among premature children with higher birth weights or presenting no evidence of cerebral injury. Hence it is concluded that the sequelae observed in the present series are due to neonatal cerebral influences rather than to prematurity itself.

Chapter VIII Sex differences are mentioned briefly. There was a majority of boys (63 per cent) but no differences were found in neonatal mortality or long-term prognosis of boys and girls. Among the neonatal fatalities there was a significantly higher incidence of cerebral oedema in the boys. No explanation can be offered for this finding.

Resumé

Formålet med arbejdet har været at vurdere neonatale, formodet cerebrale symptomers specificitet og prognostiske værdi.

I *kapitel I* gennemgås den tidligere litteratur angående cerebrale symptomer hos nyfødte med hensyn til de arbejder hvor klinik og pathologi er sammenholdt. Det fremhæves, at den kliniske diagnosticering af hjerneskader hos nyfødte er vanskelig, fordi de frembudte symptomer ofte er uspecifikke og fordi mange patienter kun frembyder meget få symptomer. De oftest registrerede symptomer er cyanose, respirationsuregelmæssigheder, bevidstheds- og tonusændringer, krampe og manglende drikkeevne. Ingen af disse er dog fundet 100 % specifikt cerebrale.

Desuden omtales tidligere arbejder om prognosen ved intracranielle, neonatale lidelser. Materialerne er vanskeligt sammenlignelige, primært p. gr. a. forskelle i udvælgelseskriterier men også p. gr. a. stor variation i efterundersøgelsesprocent og i børnenes alder ved efterundersøgelsen. Trods dette varierede frekvensen af fundne, svære cerebrale følgerelstande kun mellem ca. 10 og 30 %. Derimod viste der sig stor uenighed om, hvilke kliniske symptomer der kunne tillægges størst prognostisk betydning og nogen centydig konklusion kunne ikke udledes.

Man omtaler derefter flere nyere undersøgelsesprincipper hvor der lægges stor vægt på den neurologiske undersøgelse neonatalt. Den prognostiske betydning af disse undersøgelser vil først kunne endeligt vurderes, når langtidsefterundersøgelser har fundet sted.

I *kapitel II* beskrives eget materiale. Det består af 291 børn indlagt i neonatalperioden på børneafdelingen, Københavns Amts Sygehus i Gentofte. Udgangspunktet for undersøgelsen er journalmateriale udvalgt efter diagnoser der 1) enten sandsynliggjorde cerebral beskadigelse, hæmorrhagia intracranialis, partus difficilis seq. fractura cranii eller asphyxia neonatorum eller 2) med hvilke patienterne kunne forventes at frembyde en del af de samme symptomer som første gruppe. Disse diagnoser var atelectasis pulmonum, aspiratio ad pulmonum eller debilitas congenita. Andre patienter som kunne have haft samme symptomer men hvor anden, sikker diagnose

var givet f. eks. verificeret mb. cordis eller hiatus hernia er ikke modtaget. Det samme gælder patienter med svære neonatal icterus. Foruden de neonatale symptomer og det kliniske forløb under indlæggelsen, blev graviditets- og fødselsforløb registreret så udførligt som oplysningerne tillod.

Det hyppigst forekommende neonatale symptom var cyanose, som fandtes hos 3/4 af patienterne. Respirationsforstyrrelser og slaphed forekom hos godt 1/2, krampe hos knapt 1/4 og sitren, irritabilitet og rigiditet hos knapt 1/5 af patienterne. Symptomerne optrådte i talrige kombinationer. Gennemsnitligt havde hver patient 2,5 symptom. De præmature patienter som udgjorde 35 % af materialet, havde lidt lavere symptomfrekvens (2,3 symptom/patient) end de mature (2,7 symptom/patient). De præmature havde relativt sjældnere end de mature symptomerne krampe, sitren, irritabilitet og rigiditet.

Patienterne var indlagt i årene 1946-1955. Efterundersøgelsen fandt sted i 1958-59. Seksten børn er udgået af undersøgelsen p. gr. a. manglende oplysninger om deres senere udvikling. Tolv var døde efter udskrivelsen, men indgår i undersøgelsen, da man havde tilstrækkelige oplysninger om deres udvikling og for en dels vedkommende fyldige sektionsbeskrivelser. Om 6 børn foreligger kun skriftlige oplysninger fra forældre og/eller behandelende læge om den senere tilstand. De øvrige er undersøgt af forf. Efter undersøgelsesprocenten er således 95.

Ved efterundersøgelsen foretoges en almen klinisk og en neurologisk undersøgelse, samt en psykisk vurdering. Der blev optaget en grundig anamnese med særlig vægt lagt på psykisk, motorisk og somatisk udvikling. Desuden indhentes oplysninger om specielle undersøgelser foretaget før efterundersøgelsen (psykologisk testning, øjerundersøgelse, otologisk undersøgelse, tale-mæssig vurdering og eeg.) I enkelte tilfælde, hvor det skønmedes indiceret og var praktisk gennemførligt, blev lignende undersøgelser foranlediget gjort.

I beskrivelsen af efterundersøgelsens resultater er patienterne inddelt i neonatalt døde og 4 grupper overlevende.

122 = 44 % af patienterne døde neonatalt. Makroskopiske sektionsbeskrivelser foreligger for alle 122 patienter og der gøres rede for de påviste dødsårsager og andre abnorme fund. Hos 84 % fandtes hæmorrhagie intra-cranialt, ødema cerebrale eller en kombination heraf som primær dødsårsag. Seksten procent var døde af atelectasis pulm. og havde ingen abnorme hjernefund.

29 = 11 % (= 19 % af de patienter der overlevede neonatalperioden) havde svære cerebrale følgeretilstande: 18 patienter var oligofrene og havde svære neurologiske symptomer, 7 var oligofrene og motorisk retarderede i varierende grad og 4 var normalt begavede, men havde neurologiske symptomer. Tolv af de oligofrene patienter var døde, de fleste i alderen 2-3 år. Krampe forekom hos 16 patienter, tale-mæssig retardering hos 21 børn med-

sættelse hos i hvert fald 5 og strabismus hos 15 patienter. Der gøres rede for electroencephalografiske fund (hos 21 patienter) luftencephalografi (hos 13 patienter) og fund ved hjernesektion (hos 7 patienter) samt cranieomfangsmål (hos 20 patienter). Der blev fundet tegn på cerebral atrofi hos 21 af disse 29 patienter.

24 = 9 % (= 16 % af de patienter der overlevede neonatalperioden) havde lettere cerebrale følgetilstande i form af lettere psykisk retardering, forbigående retarderet motorisk udvikling eller trivsel gentagne krampeanfald - afebrile eller febrile - hørefekter afasi eller talemæssig retardering, forbigående hyperaktivitet i de første 1-2 leveår adfærdsvanskeligheder strabismus og enuresis. Alle havde mere end eet af disse symptomer og symptomkombinationerne var varierende. Ingen havde blivende motoriske handicaps.

30 = 11 % (= 19 % af de patienter der overlevede neonatalperioden) havde lette, formentlig cerebrale afvigelser af samme karakter som i ovennævnte gruppe, men mindre udalt, og de fleste af patienterne frembød kun et enkelt symptom. I denne gruppe var desuden 5 tilfælde af dyslexi, men ingen tilfælde af intelligensdefekt, afebrile kræmpes eller hørenedsættelse.

70 = 25 % (= 46 % af de patienter der overlevede neonatalperioden) frembød ingen abnorme fund.

Beretningen af at sætte de ved efterundersøgelsen fundne abnormiteter i relation til den neonatale tilstand diskuteres med henvisning til litteraturen. Man mener at kunne finde fuld støtte for de senere svære cerebrale symptomers vedkommende og tilstrækkelig for de lettere symptomers vedkommende til med nogen rimelighed at opretholde antagelsen af en fælles oprindelse.

I kapitel III bedømmes de neonatale symptomers diagnostiske værdi ved at sammenligne symptomerne hos følgende patienter døde neonatalt af 1) atelectasis pulm. (normal hjerne) 20 patienter 2) atelectasis pulm. og ødema cerebri, 19 patienter 3) atelectasis pulm. og hæmorrhagia intracranialis ± ødema cerebri, 61 patienter og 4) hæmorrhagia intracranialis ± ødema cerebri (normale lunger) 22 patienter.

Symptomerne. krampe, siten, irritabilitet og rigiditet forekom udelukkende hos patienter med patologiske hjernefund. For at sikre værdien af denne indtagelse er materialet suppleret med yderligere 26 patienter døde neonatalt af atelectasis pulm. Heller ikke disse patienter havde nogen af de ovennævnte symptomer.

Selv om disse symptomer i dette materiale således synes specifikt cerebrale, fandtes de på ingen måde nødvendige for at stille diagnosen hæmorrhagia intracranialis eller ødema cerebri. 46 % af de mature patienter og 79 % af de præmature med patologiske hjernefund frembød kun symptomerne cyanose, respirationsabnormiteter eller slaphed, altså de samme symptomer

som patienter døde af atelectasi pulm. Differentialdiagnosen mellem disse grupper synes meget vanskelig. Permanent cyanose sås noget hyppigere ved de rene atelectaser mens anfaldsvis cyanose var noget hyppigere blandt hjerneskadede, men begge cyanoseformer var så hyppige i begge grupper at forskellen er uden differentialdiagnostisk værdi. Derimod fandtes sene cyanoseanfald (først optrædende i 2.-3. levedøgn) udelukkende i de hjerneskadede grupper.

Det viste sig ikke muligt klinisk at skelne patienter med hjerneødem fra patienter med hjerneblødning. Alle symptomer optrådte med samme hyppighed i de 2 grupper. Der fandtes ingen forskel i optræden af permanent eller anfaldsvis cyanose eller i tidspunktet for cyanosens start. Det samme gjaldt for tidspunktet for optræden og for varighed af krampeanfald. Materialet er suppleret med 41 patienter døde neonatalt af hjerneødem uden at resultatet ændrede sig.

De neonatale symptomers betydning for den umiddelbare prognose quo ad vitam behandles i kapitel IV. Det vises, at de neonatalt døde patienter gennemsnitligt havde flere symptomer end de overlevende, således at der med øget antal symptomer hos den enkelte patient synes større risiko quo ad vitam. Dette gjaldt for både mature, hvor de neonatalt døde gennemsnitligt havde 3 1 symptom per patient og de overlevende 2,5 og for de præmature, hvor de tilsvarende tal var 2,5 og 1 7 symptom/patient. Dog sås dødsfald både blandt mature og præmature patienter som kun havde haft et enkelt symptom.

Der er foretaget opptælle over mortaliteten ved hvert enkelt neonatalt symptom, dels hvor det havde optrådt som eneste symptom (hvilket var sjældent) og dels hvor det havde været til stede sammen med andre symptomer. For præmature børn fandtes symptomerne: cyanoseanfald i første døgn, beværet og knirkende respiration, hypotoni og krampe at være alvorlige prognostiske symptomer med en mortalitet på omkring 80 % mens den for mature lå omkring 40 %. For mature børn fandtes cyanoseanfald, der først optrådte efter første døgn at være af alvorligere betydning end cyanoseanfald optrædende fra første døgn. (Mortalitet 56 % mod 27 %).

Den anfaldsvis cyanose var den hyppigste form, den fandtes hos 77 % af alle patienter med cyanose. Den permanente cyanose, der ikke hævedes inden for nogle timer samt udsættende respiration fandtes naturligt nok omvendt ensbetydende med mere neonatalt.

De mere specifikt cerebrale symptomer krampe, sitren, irritabilitet og rigiditet syntes af mindre alvorlig værdi i den umiddelbare prognose for mature (mortalitet 20-30 %) end de mere uspecifikke. For de præmature havde krampe som nævnt en alvorlig prognose. De øvrige 3 specifikke symptomer forekom så sjældent hos de præmature, at deres prognostiske betydning ikke lader sig vurdere.

I *kapitel V* vurderes de neonatale symptomers sen-prognostiske betydning ved sammenligning af disse symptomer hos patienterne i de 4 grupper overlevende (I 29 patienter med svære cerebrale følgetilstande, II 24 med lettere cerebrale følgetilstande, III 30 med lette, formentlig cerebrale afvigelser og IV 70 patienter uden senere abnorme fund)

Det vises, at det gennemsnitlige antal symptomer per patient for de fuldbårne patienter var højest i gruppe I med 3,6 symptom/patient, mens det for patienter i gruppe IV var 2,1. Desuden fandtes en klart hyppigere optræden af de specifikke symptomer i gruppe I hvor 92 % havde eet eller flere af disse symptomer mod ca. 40 % af de mature i de øvrige grupper og ca. 25 % af de præmature i samtlige grupper.

Der er foretaget opgørelse over de enkelte symptomers og symptomkombinationers betydning hos fuldbårne med følgende resultat: ved tilstedeværelse af et enkelt symptom – specifikt eller uspecifikt – fandtes relativt gode prognostiske muligheder med under 10 % s risiko for svære cerebrale følgetilstande og 50 %'s chance for fuldstændig normal udvikling (75 % hvis gruppe III med de tvivlsomme følgetilstande regnes sammen med de normale) – Praktisk taget identiske værdier fandtes ved tilstedeværelse af 2 neonatale symptomer – også selv om det ene var specifikt – og ved tilstedeværelse af 3 uspecifikke symptomer. Optrådte 2 specifikke symptomer alene syntes prognosen dårligere med ca. 30 % s risiko for svære cerebrale følgetilstande. Med stigende antal symptomer og specielt med stigende antal specifikke symptomer fandtes en tiltagende dårlig prognose: ved en kombination af mindst 3 symptomer hvormed mindst eet var specifikt, fandtes 40–60 % s risiko for alvorlige følgetilstande og op til 60–80 % hvis mindst 2 af symptomerne var specifikke.

Cyanoseanfald – i forbindelse med andre symptomer – optrædende fra første levedøgn, er fundet at have dårlig prognostisk betydning, hvis anfaldene strækker sig ud over 4 døgn. Sent optrædende cyanoseanfald syntes allerede at være af dårlig prognostisk betydning, hvis de strækker sig ud over 2 døgn mens cyanoseanfald inden for et enkelt døgn ikke syntes af alvorlig betydning.

Krampeanfald syntes forbundet med ret stor risiko for dårlig prognose, også selv om de kun optræder inden for 1–2 døgn, men oftere hvis de strækker sig ud over 3 døgn.

For præmature patienter har forholdene været meget vanskelige at vurdere, dels p. gr. a. det beskedne antal patienter der overlevede neonatalperioden, dels fordi de præmature oftest havde meget få og specielt meget få specifikke symptomer. Dog fandtes det, at helt op til 3 symptomer selv når 1 eller 2 var specifikke, ikke var ensbetydende med en dårlig prognose.

Primært for at se om etiologiske forskelle skulle ændre de neonatale symptomers diagnostiske og prognostiske værdi gøres i *kapitel VI* rede for for

hold under graviditet og fødsel samt for tilstedeværelse af asphyxi. Ved asphyxi er førstet forsinket igangsættelse af den spontane respiration efter fødslen.

Graviditetskomplikationer forekom hos 12 % af mødrene, altid så sjældent at man ikke kunne vurdere deres betydning i denne henseende. Dog fremgik det, at graviditetskomplikationer ikke på afgørende måde ændrede frekvensen af fødselskomplikationer eller af asphyxi.

Komplikationer under fødslen forekom hos 44 % d. v. s. dobbelt så hyppigt som i en normalpopulation.

35 % af børnene havde været asphyktiske. Frekvensen af asphyxi er i litteraturen i udvalgte obstetriske materialer fundet til 2-6 %. Asphyxi forekom i dette materiale dobbelt så hyppigt efter kompliceret som efter normal fødsel.

50 % af patienterne havde helt blanke graviditets- og fødselsanamneser og 2/3 af disse havde heller ikke været asphyktiske. Det fandtes, at denne gruppe patienter ikke adskilte sig i sin neonatale symptomatologi, ej heller sikkert prognostisk fra den gruppe ikke-asphyktiske patienter som havde haft komplikationer under fødslen.

Både efter normal og efter kompliceret fødsel fandtes tilstedeværelse af asphyxi at give gennemsnitligt lidt flere neonatale symptomer en tilvækst, der stort set sakket på de specifikke cerebrale symptomer. Parallelt hermed fandtes dårligere senprognose efter kortvarig asphyxi. Efter asphyxi af over 5 min. s varighed fandtes høj neonatal mortalitet.

Fødselsforløbet syntes til en vis grad at ændre de neonatale symptomers prognostiske værdi, således at en patient, som efter en normal fødsel havde haft 2-3 neonatale symptomer hvoraf 1-2 var specifikt cerebralt, oftere ville have en dårlig prognose end en patient med samme symptomkonstellation efter en kompliceret fødsel. Dette fandtes uafhængigt af graviditetsforløb eller tilstedeværelse af asphyxi.

72 af de 122 neonatalt døde børn var født på normal vis og efter ukompliceret graviditet; hos 55 % af disse fandtes intracranieel hæmorrhagi ved sektion. 41 neonatalt døde patienter havde haft komplicerede fødsler 85 % af disse havde intracranieelle blødninger. Der påvises ingen sikre symptomatologiske forskelle.

Førstefødte børn fandtes at have gennemsnitligt lidt flere specifikke symptomer end børn af flergangsfødende mødre og parallelt hermed en dårligere senprognose. Børn af ældre førstegangsfødende mødre adskilte sig ikke symptomatologisk fra børn af yngre førstegangsfødende, men havde en dårligere senprognose.

Brugen af vestimulerende midler var meget dårligt belyst og omtales der for kun kort. Det bemærkes, at børn født efter igangsat eller stimuleret fødsel, hvor forhold under graviditet og fødsel ellers var angivet normale, syn-

tes at klare sig dårligere end børn født efter ikke stimuleret, normal fødsel.

Tidligere arbejder om perinatale forholds prognostiske betydning omtales. Der fremdrages stærkt divergerende opfattelser både af fødselstraumers og asphyxis betydning, forskelle som dog nok i væsentlig grad skyldes forskelle i materialeudvælgelse. Fødselsforløbet synes ikke altsagørende men dog i visse tilfælde af primær betydning for senere cerebrale defekter. Asphyxi findes hyppigere efter komplicerede end efter normale fødsler og fører i sine svære grader ofte til mors neonatalt og giver i sine lettere grader ret ofte cerebrale følgetilstande. Dog synes neonatale cerebrale symptomer at give sikrere prognostiske holdepunkter end fødselsforløb og asphyxi.

I *kapitel VII* omtales præmaturitetsproblemet. Præmaturitetsfrekvensen var meget høj (35 % mod ca. 7 % i normalbefolkningen) og de præmatures neonatale mortalitet betydeligt højere (70 %) end de matures (31 %) højere jo lavere FV.

Dermod påvises ingen sæn prognostiske forskelle mellem præmature og mature (31 % af de præmature og 35 % af de mature havde svære eller lettere cerebrale følgetilstande).

Symptomatologisk adskilte de præmature sig fra de mature ved at frembyde færre neonatale symptomer: dette vises at blive mere udtalt jo lavere FV.

Der gives en oversigt over tidligere arbejder om præmatures prognose. Også disse arbejder er vanskeligt sammenlignelige primært p. gr. a. forskelle i materialeudvælgelseskriterier og efterundersøgelsesprocent. Dog fremgik det, at der blandt præmature, som neonatalt havde haft cerebrale symptomer eller som havde haft meget lav FV fandtes højere procent af patienter med cerebrale følgetilstande end blandt præmature med højere FV eller uden neonatale tegn på cerebral skade. Man konkluderer derfor at de påviste følgetilstande i dette materiale skyldes de neonatale, cerebrale påvirkninger snarere end præmaturiteten som sådan.

Kapitel VIII Forholdet mellem drenge og piger omtales desuden kort. Der var i materialet en overvægt af drenge men der påvises ingen forskel i neonatal mortalitet eller i sæn-prognose. Blandt de neonatalt døde fandtes en significant større frekvens af hjerneødem hos drenge end hos piger. Det fandtes ikke muligt at give nogen forklaring herpå.

Case Reports

No. 1 (record 258/3/1947)

A boy born at term in private clinic, on June 25, 1947 to 39 year old multipara following an uncomplicated pregnancy. The delivery was induced by quinine and injections; the course was uncomplicated. The infant was not asphyxiated, but as admitted to the Department of Paediatrics (DPG) The Copenhagen County Hospital at Gentofte (KASG) on the second day because of poor sucking. During the third day of life he suffered several convulsions associated with short spells of fever. No other abnormalities were noted except poor growth for about two weeks. He was discharged when 16 days old apparently in good condition.

Diagnosis: eclampsia, intracranial haemorrhage.

At the age of about one year he was referred to the Out Patient Department of the University Clinic of Paediatrics at Rigshospitalet (RH) because of retarded development.

Examination at this time showed him to be severely retarded. He was unable to sit up or to hold his head. He had bilateral tightness of the heel cord. His muscle tone could not be assessed. There was pronounced squint. Prior to admission he had shown occasional "twinklings". Placement under the National Service for the Mentally Retarded (Statens Anstaltsforborg - SA) was recommended, the diagnosis being mental deficiency sequelae of intracranial haemorrhage. Additional diagnoses were: symptomatic epilepsy, spastic quadriplegia.

There was no family history of cerebral disease.

It is not known whether the recommendation was followed or not.

The patient died in 1949 when about 2 years old. Post mortem was not performed.

No. 2 (1193/3/1950)

A girl, born at term in a private clinic, on March 12, 1949 to a 37-year old primipara, following a normal pregnancy. The delivery lasted for more than two days, and forceps were used because of feeble labour. Labour-inducing drugs had apparently not been given. No information is available on the use of morphine. The cord was wound around the child's neck five times; she did not breathe for seven minutes, was given 0.3 ml lobeline and immediately transferred to the DPG, where she remained for 33 days. On the first day of life she was given nikethamide and lobeline. During the first week she had repeated convulsions, was rigid and sucked poorly. Her general condition was poor during the first month, then improved, and on discharge it was described as good.

Diagnosis: intracranial haemorrhage.

The parents suspected that something was wrong when the child was unable to focus or sit up at the age of 7-8 months. When she was one year old, they consulted the Neuropaediatric Out Patient Clinic (NPO) of the RH, where she was subsequently treated.

She sat at 14 months, stood with support at two years, walked with support at

5½ years and took a few steps unaided at 6½. Her motor pattern was characterized by pronounced imbalance as well as poor coordination of all extremities.

Mental development was severely retarded she had a violent temper and was hard to keep occupied. At the age of 8 years she was placed under the S.A. She attended a daily kindergarten for retarded children.

During her second year of life she had several convulsions in association with fever. At the age of seven years she again had repeated generalized clonic convulsions unprecipitated by fever. Anti-convulsant therapy was initiated at this time. On the last examination at the RH at the age of 8 years she had been seizure-free for about 6 months. EEG first performed at 4 years of age, was severely abnormal, with spikes and spiko-waves, especially in the right parietal tracing. The last EEG, at 8 years, was still severely abnormal.

Speech development had been relatively good. She began to form sentences at the age of 2 years and talked quite intelligibly by the time she was seven. Her hearing was felt to be normal. She had a squint and nystagmoid eye movements, and her vision was apparently diminished.

There was no family history of cerebral disease.

At follow-up, when she was about 10 years old her general condition was good. Her height was 5 cm above average however her weight was 6 kg below normal. Mental development appeared severely retarded. However her speech was essentially normal apart from a stutter and a somewhat limited vocabulary. The squint and nystagmoid eye movements persisted. Her head was small, with a circumference of 47.5 cm. Her motor pattern was rather ataxic and neurological examination revealed additional slight spasticity. There were no contractures of the limbs.

Diagnoses: spastic quadriplegia, ataxia, mental deficiency microcephaly symptomatic epilepsy strabismus.

No 3 (582/3/1950)

A boy born on Sept. 22, 1950, to a primipara. The pregnancy had been uncomplicated. The delivery took place at home at term and was normal. No record of labour inducing methods or morphia. The patient was asphyxiated for "a few minutes" he was treated with contrast baths and injections of unknown type and immediately admitted to the DPGs, where he remained for 24 days. He was very flaccid on admission, but soon developed rigidity and hyperirritability. During the first 6 days several convulsions occurred. A lumbar puncture was performed the spinal fluid was straw-coloured. The rigidity eventually diminished his general condition improved and he started to gain weight.

Diagnosis: intracranial haemorrhage.

At 6 weeks of age the convulsions recurred and he was readmitted to the DPGs. On admission his general condition was poor and there was pronounced rigidity. Lumbar puncture again was performed. The spinal fluid was yellow. Two days later he was transferred to the neurosurgical department of the RH. However before further investigation could be carried out, his condition deteriorated and because of severe signs of ileus he was transferred to the Dept. of Paediatrics at the RH where he died the following day. Age at death was two months.

There was no history of cerebral disease in the family.

Post mortem revealed volvulus colon sigmoidalis and perforation of the rectum. Brain section showed multiple cysts of varying age, some quite recent. In some areas of the cortex there was total destruction of ganglion cells with proliferation of glial tissue, but no inflammatory processes.

Diagnoses: spastic quadriplegia and symptomatic epilept.

No 4 (1403/3/1951)

A girl, a first child, born on April 20, 1951. The pregnancy had been normal until 3 weeks before delivery when the mother sustained an abdominal injury followed by

suspect, but no further complaints. The delivery took place at home and was induced by injections. It was reported to have been prolonged, and the heart sound had been affected towards the end. The patient exhibited prolonged asphyxia and did not cry until an hour after birth. She was treated with contrast baths and stimulant injections. On the second day she was admitted to DPGC because of flaccidity; she also had grunting respiration and was given oxygen for several hours. Over the next few days the flaccidity was succeeded by hypertonicity which, however, had disappeared when she was discharged in apparently good condition after 16 days.

Diagnostic intracranial haemorrhage.

Delayed development was suspected by the parent when she was unable to sit up at the age of twelve months and also had clumsy hand movements. Her growth was good despite difficulty in swallowing and later also in chewing.

She could sit alone when 18 months old, walked with support at three years and alone when about 4 years. Her gait was unsteady broad-based and with high knee-movements. Her hand movements were also unsteady.

When nearly 3 years old she was examined at the NPO of the RH, where her condition was diagnosed as quadriplegia with mild stasia. On re-examination at the age of 4 the former diagnosis was abandoned, the latter maintained.

Her mental development, as judged by her ability to comprehend situations, was essentially normal at the age of 5 and at the last examination, at the age of 7 her condition had further improved, mentally as well as somatically. She had not, however, attained the development appropriate to her age. Her speech was obviously retarded, she had prattled by 6 months, said a few words at 3 years, but at the age of 7 was still unable to form sentences. Speech comprehension was correspondingly poor. She had repeatedly been examined by a speech therapist from the Stal Institute for Speech Disorders, who diagnosed receptive and expressive aphasia. An otologist found her hearing to be slightly diminished at the age of 7 years.

An evaluation of her mental condition had been difficult owing to multiple handicaps. Proper testing was not performed. At 10 years an application submitted for education at a State School for the mentally retarded was rejected, as the child was considered too bright. At the age of 13 she was rejected at school for the handicapped due to feeble-mindedness. In the same year she was accepted for a trial period as a pupil at the State Institute for Speech Disorders.

Diagnosis: mental deficiency (7), stasia, receptive and expressive aphasia, mild hearing loss.

There was no history of cerebral disease in the family.

EEG: 1) at 3 years: severely abnormal with generalized spikes, >at predominantly posteriorly over the left occipital region. 2) at 6 years: severely abnormal, very irregular tracing with changes in frequency. Considerable spike activity mainly in the form of single spikes of high amplitude, often universally synchronous, but with a clear predominance over the right parieto-occipital region. No accentuation of the changes was seen during photic stimulation. During sleep the focal character was somewhat less pronounced and the abnormal pattern consisted of spike-waves of 2-3 per sec. of very high amplitude.

1 5 (20097 3.1932)

A boy born on Feb. 26, 1932 to a 32 year old primipara following normal pregnancy. The delivery took place in private clinic. It was induced, presumably on the suspicion of rachitic pains; it was prolonged, but otherwise uncomplicated. The BW was 3800 g. There was asphyxia for a few minutes, during which lobeline, 10g was given. On the second day the infant was transferred to DPGC suspected of intracranial injury because of poor sucking and tremor. During the first few days he was found to be rigid; however, the tone subsequently became normal. The neonatal period was complicated by pyloric stenosis, for which surgery was successfully performed. He was discharged after 36 days, apparently in good condition, though jaundice was noted.

Diagnosis. intracranial haemorrhage.

During the first 10 months of life there was practically no motor or mental progress, however his growth was satisfactory. The nystagmus persisted and a squint was also noticed.

At ten months he was readmitted to the DPGs with severe meningitis and a history of convulsions for one week. During the acute illness he developed severe spasticity of all four limbs as well as a pronounced hydrocephalus. He remained an in-patient for one year during which time his progress was unsatisfactory. There was no motor development and he was unresponsive. He was treated with phenobarbitone for acute restlessness. When about two years old he was placed in an institution for mentally defectives (Andersvænge). During the next six months there were four generalized seizures and numerous episodes of withdrawal or loss of consciousness lasting as long as 24 hours. After going downhill he died aged $2\frac{1}{2}$ years from bacillary dysentery.

Post mortem was not performed owing to the refusal of the parents.

Diagnosis. Idiocy, acquired hydrocephalus, acquired quadriplegia, symptomatic epilepsy strabismus.

There was no family history of cerebral disease.

No 6 (2801/3/1952)

A boy born as second twin on May 4, 1952, to a multipara following an uncomplicated pregnancy. The delivery took place at home and apparently was normal. The twins were monozygotic; the brother was well. The patient was admitted to the DPGs at 11 days because of poor growth which persisted for two weeks. Subsequently his growth was satisfactory and the infant was otherwise normal. He was discharged after 25 days in apparently good condition.

Diagnosis. congenital debility

The patient's development was evidently slower than that of the twin brother. At six months he experienced a convulsion associated with fever and six months later another convulsion, this time unassociated with fever. At 18 months he was readmitted following a third, afebrile, seizure. He was found to be physically and mentally retarded and was thought to have a mild quadriplegia.

EEG at 18 months showed multiple focal abnormalities suggesting generalized organic brain damage.

He walked at about $2\frac{1}{2}$ years and said single words at about two years. At about three years he experienced a severe convulsion following premedication prior to surgery for hydrocele. Hereafter there was pronounced leftsided hemiparesis and aphasia. At about the age of four he was admitted to a neurosurgical department, Bispebjerg Hospital. A ventriculography was performed, revealing enlargement of the entire ventricular system, more so on the right side. There was copious air over the convexity on the left side, none over the right. Radiological diagnosis was cerebral atrophy. Arteriography on the right side showed shift to the right of the anterior cerebral artery, no malformation, the blood flow was slower than normal (no explanation).

In spite of anti-convulsant drugs the child had seizures approximately twice a year.

The parents did not wish to attend the follow-up examination.

There was no familial history of cerebral disease.

Diagnosis: Mental deficiency, acquired aphasia, congenital mild spastic quadriplegia, acquired left sided spastic hemiplegia, symptomatic epilepsy.

No 7 (2735/3/1952)

A boy born to a primipara on May 13, 1952, following an uncomplicated pregnancy. The delivery took place in a private clinic, was induced at term and energetically stimulated. Moreover pethidine was given on two occasions. The course was otherwise uncomplicated and not prolonged. The child was asphyxiated for 5 minutes and was brought to the DPGs approximately one day old because of persisting cyanosis.

On admission he was also flaccid. The cyanosis subsided following oxygen therapy and he was discharged three days later in apparently good condition.

Diagnosis: asphyxia neonatorum.

The parents suspected retarded development when the child was unable to sit up at the age of one year. They also found him mentally retarded. He was brought to the NPO of the RH, where he was followed-up at intervals. On the last occasion, at the age of 6½ years, he showed moderate spasticity most pronounced in the legs.

He is able to sit alone at 15 months, began to walk alone at 29 months and eventually walked fairly well. Mental development was also retarded. Psychological testing had been attempted repeatedly but was difficult. When last tested, at the age of 6½, the child's intelligence was found to equal that of a 4-5 year old. He also had speech disorder. On the last examination his vocabulary was very limited and the formation of sentences was poor. His hearing was considered to be normal, his vision was good, but he had a squint. Head circumference on all examinations had been below the limit of normal; the shape of his head was otherwise normal.

No family history of cerebral disease was elicited.

Diagnosis: mental deficiency, spastic diplegia, speech retardation, microcephaly, convergent strabismus.

No. 8 (G691/3/1952)

A boy first child, born at term in a private clinic on May 19, 1952, following an uncomplicated pregnancy. The delivery was induced and took a normal course, however manual expulsion was performed. There was asphyxia for a few minutes, during which lobeline was given. He was immediately referred to the DPGs suspected of tetralogy of Fallot. On admission he was restless, trembling and rigid. From the second to the fourth day repeated attacks of cyanosis and convulsion occurred. His growth was poor during the first two weeks, but eventually improved. When discharged after 3 weeks there was still moderate rigidity.

Diagnosis: intracranial haemorrhage.

At home he was restless and therefore referred to the OP of the DPGs 3 months old. He exhibited spasticity in all four limbs.

His motor development was very unsatisfactory. He was never able to sit up or stand and control of headmovements was poor. His growth was slow and he was difficult to feed. He exhibited squint. He was also mentally retarded, though he did appear to have some contact with his surroundings. He could smile, and at 18 months was able to say a few words. At this time he came under the care of S.A. and was placed in an institution (Andervenne), where he died one year later.

There was no family history of cerebral disease.

Brain section (by Dr. Erna Christensen): Weight of the fixed brain 1050 grams. Moderate dilatation of the ventricles, no necrotic processes, but some atrophy of the basal ganglia. Sclerosing pyknotic ganglion cells, particularly in the putamen and the adjacent thalamus, with occasional intracellular calcification. Degeneration of myelin sheaths in the same area. Normal ganglia in the hypothalamus. Normal cortex, medulla oblongata and cervical medulla. Diagnosis: congenital dysplasia of the cerebellum, chronic degeneration of the basal ganglia. Possible anoxic aetiology.

No. 9 (1470/3/1952)

A boy born in hospital on Dec. 6, 1952, to a 16 year old unmarried primipara. During the delivery which was uncomplicated, quinine and pituitrin was administered. The BW was 1540 g. There was no asphyxia. Immediate referral to the DPGs because of low BW. On admission the child's respiration was grunting, and during the next 25 days there were numerous severe cyanotic attacks of diminishing frequency during which he was considered moribund several times. In such cases lobeline was given. He received oxygen for four weeks, after which it was withdrawn over three weeks under regular eye observation. Four days before given was discontinued, and he

Diagnosis: Intracranial haemorrhage.

During the first 10 months of life there was practically no motor or mental progress, however his growth was satisfactory. The nystagmus persisted and a squint was also noticed.

At ten months he was readmitted to the DPGs with severe meningitis and a history of convulsions for one week. During the acute illness he developed severe spasticity of all four limbs as well as a pronounced hydrocephalus. He remained an in-patient for one year during which time his progress was unsatisfactory. There was no motor development and he was unresponsive. He was treated with phenobarbitone for acute restlessness. When about two years old he was placed in an institution for mentally defectives (Andersvænge). During the next six months there were four generalized seizures and numerous episodes of withdrawal or loss of consciousness lasting as long as 24 hours. After going downhill he died aged 2 $\frac{1}{2}$ years from bacillary dysentery.

Post mortem was not performed owing to the refusal of the parents.

Diagnosis: idiocy acquired hydrocephalus, acquired quadriplegia, symptomatic epilepsy strabismus.

There was no family history of cerebral disease.

No 6 (2801/3/1952)

A boy born as second twin on May 4 1952, to a multipara following an uncomplicated pregnancy. The delivery took place at home and apparently was normal. The twins were monozygotic; the brother was well. The patient was admitted to the DPGs at 11 days because of poor growth which persisted for two weeks. Subsequently his growth was satisfactory and the infant was otherwise normal. He was discharged after 25 days in apparently good condition.

Diagnosis: congenital debility

The patient's development was evidently slower than that of the twin brother. At six months he experienced a convulsion associated with fever and six months later another convulsion, this time unassociated with fever. At 18 months he was readmitted following a third, afebrile, seizure. He was found to be physically and mentally retarded and was thought to have a mild quadriplegia.

EEG at 18 months showed multiple focal abnormalities suggesting generalized organic brain damage.

He walked at about 2 $\frac{1}{2}$ years and said single words at about two years. At about three years he experienced a severe convulsion following premedication prior to surgery for hydrocele. Hereafter there was pronounced left-sided hemiparesis and aphasia. At about the age of four he was admitted to a neurosurgical department, Bispebjerg Hospital. A ventriculography was performed, revealing enlargement of the entire ventricular system, more so on the right side. There was copious air over the convexity on the left side, none over the right. Radiological diagnosis was cerebral atrophy. Arteriography on the right side showed shift to the right of the anterior cerebral artery no malformation the blood flow was slower than normal (no explanation).

In spite of anti-convulsant drugs the child had seizures approximately twice a year. The parents did not wish to attend the follow-up examination.

There was no familial history of cerebral disease.

Diagnosis: Mental deficiency acquired aphasia, congenital mild spastic quadriplegia, acquired left-sided spastic hemiplegia, symptomatic epilepsy

No 7 (2735/3/1952)

A boy born to a primipara on May 13 1952, following an uncomplicated pregnancy. The delivery took place in a private clinic, was induced at term and energetically stimulated. Moreover pethidine was given on two occasions. The course was otherwise uncomplicated and not prolonged. The child was asphyxiated for 5 minutes and was brought to the DPGs approximately one day old because of persisting cyanosis.

On admission he was also flaccid. The cyanosis subsided following oxygen therapy and he was discharged three days later in apparently good condition.

Diagnosis: asphyxia neonatorum.

The parents suspected retarded development when the child was unable to sit up at the age of one year. They also found him mentally retarded. He was brought to the NPO of the RH, where he was followed-up at intervals. On the last occasion, at the age of 6½ years, he showed moderate spasticity most pronounced in the legs.

He was able to sit alone at 15 months, began to walk alone at 29 months and eventually walked fairly well. Mental development was also retarded. Psychological testing had been attempted repeatedly but was difficult. When last tested, at the age of 6½, the child's intelligence was found to equal that of a 4-5 year old. He also had speech disorder. On the last examination his vocabulary was very limited and the formation of sentences was poor. His hearing was considered to be normal, his vision as good, but he had squint. Head circumference on all examinations had been below the least of normal, the shape of his head was otherwise normal.

No family history of cerebral disease was elicited.

Diagnosis: mental deficiency spastic diplegia, speech retardation, microcephaly convergent strabismus.

No. 8 (2091/3/1952)

A boy first child, born at term in a private clinic on May 19 1952, following an uncomplicated pregnancy. The delivery was induced and took a normal course; however, manual expulsion was performed. There was asphyxia for few minutes, during which lobeline was given. He was immediately referred to the DPGs suspected of umbilical rupture. On admission he was restless, trembling and rigid. From the second to the fourth day repeated attacks of cyanosis and convulsions occurred. His growth was poor during the first two weeks, but eventually improved. When discharged after 3 weeks there was still moderate rigidity.

Diagnosis: intracranial haemorrhage.

At home he was restless and therefore referred to the OP of the DPGs 3 months old. He exhibited spasticity in all four limbs.

His motor development was very unsatisfactory. He was never able to sit up or stand and control of headmovements was poor. His growth was slow and he was difficult to feed. He exhibited squint. He was also mentally retarded, though he did appear to have some contact with his surroundings. He could smile, and at 18 months was able to say few words. At this time he came under the care of S.A. and was placed in an institution (Andervrucht), where he died one year later.

There was no family history of cerebral disease.

Brain section (by Dr. Erns Christensen): Weight of the fixed brain 1050 grams. Moderate dilatation of the ventricles, no necrotic processes, but some atrophy of the basal ganglia. Sclerosing pyknotic ganglion cells, particularly in the putamen and the adjacent thalamus, with occasional intracellular calcification. Degeneration of myelin sheaths in the same area. Normal ganglia in the hypothalamus. Normal cortex, medulla oblongata and cervical medulla. Diagnosis: congenital dysplasia of the cerebrum, chronic degeneration of the basal ganglia. Possible anoxic aetiology.

N 9 (1470/3/1952)

A boy born in hospital on Dec. 6, 1952, to 16 year old unmarried primipara. During the delivery which was uncomplicated, quinine and pituitrin was administered. The BW was 1580 g. There was no asphyxia. Immediate referral to the DPGs because of low BW. On admission the child's respiration was grunting, and during the next 25 days there were numerous severe cyanotic attacks of diminishing frequency during which he was considered moribund several times. In each case lobeline was given. He received oxygen for four weeks, after which it was withdrawn over three weeks under regular eye observation. Four days before oxygen was discontinued ophthalm-

scopy was normal, but five days after its discontinuation there was marked retrolental fibroplasia. After subsiding to some extent it became stationary. After a while growth became normal, and the infant was discharged after 75 days in apparently good condition, apart from the eye changes. He was placed in a private foster home.

Diagnoses: prematurity congenital debility retrolental fibroplasia.

The foster parents consulted the DPGs when the boy was 6 months old because of pronounced strabismus. He was found to be severely retarded, physically as well as mentally. He had a severe spastic quadriplegia, which was attributed to intracranial haemorrhage. There was also a question of possible microcephaly. The retrolental fibroplasia persisted.

At 11 months he was seen at the NPO of the RH. The diagnoses were confirmed except for the eye changes, which had disappeared.

EEG at one year showed a severe focal dysrhythmia with spikes in the left temporal region.

He achieved a developmental quotient of 30 (according to Bühler). One month later he was admitted to hospital (Norre Hospital) and at the age of 4 years was placed in an institution under SA (Rødbygård). He died at the age of 4 years and 3 months having failed to develop physically in any respect and mentally to only a slight degree. His DQ had remained at about 30 on later tests. His growth was poor: he had difficulty in swallowing and was unable to take anything but Biquil food. His vision was deficient.

There was no history of cerebral disease in the family.

Post mortem was not performed.

Diagnoses: Idiocy spastic quadriplegia, microcephaly strabismus.

No. 10 (1025/3/1953)

A boy born as a first child on Jan. 15 1953 following a normal pregnancy. Delivery took place at home at term and was prolonged. There is no record of the use of labour inducing drugs or morphia. There was prolonged asphyxia, and the child did not cry until one hour after birth. There is no record of what resuscitation methods were used. He was first admitted to hospital 13 days later because of flaccidity restlessness and poor growth. On admission he was irritable and flaccid and sucked poorly from the 14th to the 18th day there was considerable trembling and repeated convulsions. Thereafter the child recovered somewhat and his growth improved. When discharged, after one month's stay he was still rather apathetic, however and appeared withdrawn. During admission his head circumference increased by 3 cm (1 cm more than normal rate). Continued follow-up was recommended.

Diagnosis: intracranial haemorrhage.

The child was readmitted at the age of 3 months. His growth meanwhile had been good, but he had been restless and rigid with occasional opisthotonus. He did not recognize his parents and he did not focus. On examination he was found to be rigid and listless. The rigidity was more pronounced on the right side. Head circumference had increased by 10 cm since birth (against a normal increase of 5 cm) and was clearly greater than normal. Ventriculography was performed at 4 months and revealed hydrocephalus with shift to the right of the enlarged ventricular system. On subsequent craniotomy a cyst over the left hemisphere was evacuated. The course was uneventful. Repeat air encephalography at the age of 5 months, again showed dilatation of the ventricular system. The condition did not improve, and the child remained restless and rigid. The temperature fluctuated. Death occurred in hyperpyrexia when the child was 6½ months old. Post mortem was not performed.

There was no family history of cerebral disease.

Diagnoses: Internal hydrocephalus, operated spastic quadriplegia.

No. 11 (1587/3/1953)

A boy born at term at the RH on April 7 1953 to a multipara, who had suffered from epilepsy since she was 19. The delivery was prolonged, forceps were used. BW

was 4300 grams. The infant was asphyxiated for six minutes and cyanosed for the first few hours. He was trembling and rigid and suffered repeated convulsions during the next few days. The rigidity gradually diminished and had disappeared by the time the infant was transferred to the DPGs at the age of 18 days. He remained in this department only three days and on discharge his condition apparently was good.

Diagnosis: sequelae of difficult birth.

During the following six months he exhibited repeated seizures, until anticonvulsant therapy was instituted.

EEG, at 6 months, showed severe dysrhythmia with numerous spikes and spike-wave.

Both mental and motor development were severely retarded. During the first year of life he was examined at several hospitals, where the diagnoses of mental deficiency and cerebral palsy were made, the type of paresis, however, was difficult to determine; spastic athetosis, ataxia and hypotonia were all considered. At the age of two years he was put under SA and two years later placed in an institution (Ebbesrådgård), where he still remained at the time of follow-up, when he was 4½ years old. A conclusive neurological diagnosis was difficult even at this point. His muscle tone varied considerably: his motor pattern was that of an infant; and though able to sit up, he could not stand. The picture was somewhat ataxic. There was considerable mental deficiency. He was pleased to have company but recognized none and could not be engaged in any kind of activity. A convergent strabismus was present.

Diagnosis: idiocy cerebral palsy ataxia? symptomatic epilepsy convergent strabismus.

No. 12 (7284/3/1954)

A girl born in private clinic on March 24, 1954, to 29 year old primipara. The delivery was induced at term and was normal, pethidine was given, however. The infant was asphyxiated for 20 minutes, in the course of which she was given cocaine, lobeline and alternating hot and cold baths. She was immediately transferred to the DPGs suspected of intracranial hemorrhage. She suffered a few cyanotic attacks during the first 24 hours. A cephaloematoma was found in the right occipital region, but otherwise she was normal and hence was discharged on the third day.

Diagnosis: asphyxia neonatorum, congenital debility.

During the early months of life she exhibited frequent tonic-clonic seizures, sometimes several times daily. Despite intensive antiepileptic therapy the seizures persisted prompting re-examination at the age of three months. At that time she exhibited pronounced motor hyperactivity and rigidity and at the age of 6 months diagnosis of spastic quadriplegia was made. She never attained essential motor functions. When she was last seen, at the age of 12 years she could neither sit, nor walk and was completely helpless. She was severely mentally defective, almost unresponsive, had no speech nor comprehension of speech. She was microcephalic, extremely emaciated, but of normal height and pubescence. Though under the care of SA she nevertheless had been looked after at home, until she was institutionalized (at the Children's Hospital in Vanggårde) at the age of 12 years. Until that time she had been treated at the NPO of the RH.

N family history of cerebral disease was elicited.

Diagnosis: mental deficiency spastic quadriplegia, symptomatic epilepsy microcephaly convergent strabismus.

EEG had been performed as follows: 1) at 9 months: normal, 2) at 20 months: normal, 3) at 26 months: severely abnormal, 4) at 3 years: severely abnormal (1.3 per second focus with bifrontal spikes plus isolated spikes in the left hemisphere, 5) at 5 years: severely abnormal with paroxysmal pattern, 2-5 per second activity of high amplitude, generalized admixture of spikes; slight amplitude predominance on the left side, or depression of activity on the right side.

PEG was performed 1) at 15 months, showing moderate generalized enlargement of the ventricles, 2) at 26 months showing generalized atrophy of predominantly cortical location.

No 13 (781/3/1954)

A girl, born at term at home on April 8, 1954 to a multipara, who had suffered hyperemesis during the first four months of the pregnancy. The delivery was stimulated by injections and was very quick. The infant was not asphyxiated, but was admitted to the DPGs on her second day of life owing to the occurrence of convulsions. On admission she was found to be restless and rigid, with grunting respiration. Several seizures occurred on the day of admission and the following day but not again. On discharge, at 14 days, she was however still restless, screaming and somewhat rigid.

Diagnosis: intracranial haemorrhage.

Following discharge the parents suspected cerebral damage, and due to retarded development the child was brought to the NPO of the RH at the age of 6 months. A diagnosis was made of spastic quadriplegia, presumed mental deficiency and microcephaly. Moreover there were nystagmoid eye movements and a squint.

PEG at the age of 14 months revealed severe generalized dilatation of the ventricular system.

Mental development remained severely retarded, though she was not completely unresponsive. Motor development was also severely retarded. At the age of 18 months she was able to sit up supported, but never unsupported. From the age of 12 months she exhibited frequent spells of rapid twitching, often occurring several times daily and provoked by noise. She was treated with phenobarbitone.

EEG was characterized by 2-3 per second activity of high amplitude, more so over the right hemisphere and bilaterally. There were a number of spikes and spike-waves (single) over the right fronto-temporal region. (The record was unlike hyper-rhythmia).

When 18 months old she was placed under S.A. and at about 2 years she was institutionalized (Children's Hospital at Nyborg). She died there at the age of 2 1/2 years.

There was no history of cerebral disease in the family.

Diagnoses: mental deficiency quadriplegia, symptomatic epilepsy microcephaly and strabismus.

Brain section was performed by Dr Erna Christensen. The brain weighed 600 grams following fixation. Its shape was normal, though the cerebrum was considerably smaller than normal. Microgyri were seen all over the convexity though not of uniform distribution. On the lower aspect of the right frontal lobe the gyri were flattened presumably due to enlargement of the anterior horn. The leptomeninges were not thickened. The vessels showed no definite changes. The cerebellum was of normal size and had normal gyri. Frontal section revealed spongy brain tissue with networks of varying size. The degeneration was most pronounced on the convexity and in the anterior two-thirds of the cerebrum there was atrophy of the gyri in the parieto-occipital lobes, but no polyporencephaly was observed. The ventricles were severely enlarged. The cystic necrotic processes had invaded the insula and the lateral areas of the corpus striatum in both sides. In the area of the thalamus, at the level of the massa intermedia bilateral atrophy was present in the upper median portions in the form of yellowish necrotic processes. Yellowish discoloration was not observed elsewhere. The remaining areas of the basal ganglia were sclerotic, with blurred outlines. The aqueduct and the fourth ventricle were not enlarged. There was slight granulation in the ependyma on the walls of the lateral ventricles and possibly also in the fourth ventricle. The cerebellum, pons and medulla oblongata were macroscopically normal on the sectioned surfaces.

Pathological diagnosis: pronounced polyporencephaly due to cerebral anoxia.

No. 14 (26001/205/1955)

A girl born in hospital on March 8, 1955, to a 30 year old primipara following normal pregnancy. The delivery was normal, BW was 3800 g. No asphyxia. Admitted to the DPGs on the second day because of convulsion and suspected intracranial haemorrhage. The convulsion did not recur, but she remained rigid, trembling and with a high-pitched cry until the 10th day. There was a cephalhaematoma in the right side. The eye movements were nystagmoid, and ophthalmoscopy showed retinal haemorrhages. On discharge, 14 days later her condition was good, but follow-up was recommended.

Diagnosis: intracranial haemorrhage.

Re-examination at NPO of the RH at 3 months revealed spasticity in all four limbs, restlessness, tremor sensitivity to noise and a squint. Head circumference was normal at this time, but at about 2 years of age it was just below average, and then lost track at well over four years, it was well below the normal limit. At 9 to 10 months she had episodes of jerking in the legs, which did not recur however. From her third month she was treated with phenobarbitone and myosidine. Her mental development was slow. At 4 years her speech comprehension was poor and she was able to make only a few sounds. Growth was good during the early months of life, but subsequently poor. Motor function was very defective; when seen last at four years she was unable to sit up alone.—There was no family history of cerebral disease.

Diagnosis: mental deficiency spastic quadriplegia, microcephaly strabismus.

No. 15 (26262/3/1955)

A girl, born at term in a private clinic on March 11 1955 to a primipara, who within the first month of pregnancy had been operated on for corpus luteum cyst. Otherwise the pregnancy was normal. The prolonged delivery was stimulated by 13 or 14 injections because of lack of progress. The heart sound eventually became affected, and the infant was delivered by forceps. She was asphyxiated for an unknown length of time and was admitted to the DPGs during her second day of life because of convulsions and suspected intracranial haemorrhage. On admission she was rigid, restless and screaming, and during the second to fifth day she experienced numerous convulsions. There were also several episodes of harlequin colour change. The rigidity subsided within eight days. However her condition was described as unsatisfactory at discharge after 26 days, though no particulars were given. The outlook was considered doubtful.

Diagnosis: intracranial haemorrhage, nystagmus, strabismus.

Her development was severely retarded. At 7 months a diagnosis of spastic quadriplegia was made on O.P. examination at the DPGs. Subsequently she was treated at other hospitals. She achieved no motor function and had hardly any contact with her surroundings. She could smile and focus, however. Her hearing was thought to be impaired and she did not talk. She was very restless. At about 18 months she experienced two episodes of convulsions and from the age of two, or two-and-a-half the exhibited repeated seizures.

EEG at 1 year 7 months showed an atypical pattern with absence of activity in central-parietal and central tracings in sleep as well as waking record. Frontal and temporal tracings revealed spikes, more pronounced on the left side.

PEO at the same age disclosed excessive enlargement of the lateral ventricles, the left being larger than the right. No cortical air was seen.

Her growth was poor and she had to be fed by tube most of the time. At about 18 months she was put under S.A. and at about 2 years she was placed in an institution (Karensundhed), where she died of broncopneumonia some seven months later.

There was no family history of cerebral disease.

Diagnosis: mental deficiency spastic quadriplegia, symptomatic epilepsy microcephaly

Brain section was performed by Dr Erna Christensen. The weight of the fixed

PEG was performed 1) at 15 months, showing moderate generalized enlargement of the ventricles; 2) at 26 months showing generalized atrophy of predominantly cortical location.

No 13 (781/3/1954)

A girl, born at term at home on April 8, 1954 to a multipara, who had suffered hyperemesis during the first four months of the pregnancy. The delivery was stimulated by injections and was very quick. The infant was not asphyxiated, but was admitted to the DPGs on her second day of life owing to the occurrence of convulsions. On admission she was found to be restless and rigid, with grunting respiration. Several seizures occurred on the day of admission and the following day but not again. On discharge, at 14 days, she was however still restless, screaming and somewhat rigid.

Diagnosis: Intracranial haemorrhage.

Following discharge the parents suspected cerebral damage, and due to retarded development the child was brought to the NPO of the RH at the age of 6 months. A diagnosis was made of spastic quadriplegia, presumed mental deficiency and microcephaly. Moreover there were nystagmoid eye movements and a squint.

PEG at the age of 14 months revealed severe generalized dilatation of the ventricular system.

Mental development remained severely retarded, though she was not completely unresponsive. Motor development was also severely retarded. At the age of 18 months she was able to sit up supported, but never unsupported. From the age of 12 months she exhibited frequent spells of rapid twitching, often occurring several times daily and provoked by noise. She was treated with phenobarbitone.

EEG was characterized by 2-3 per second activity of high amplitude, more so over the right hemisphere, and bifrontally. There were a number of spikes and spike-waves (single) over the right fronto-temporal region. (The record was unlike hypsar rhythmia).

When 18 months old she was placed under SA and at about 2 years she was institutionalized (Children's Hospital at Nyborg). She died there at the age of 2½ years.

There was no history of cerebral disease in the family.

Diagnoses: mental deficiency quadriplegia, symptomatic epilepsy microcephaly and strabismus.

Brain section was performed by Dr Erna Christensen. The brain weighed 600 grams following fixation. Its shape was normal, though the cerebrum was considerably smaller than normal. Microgyri were seen all over the convexity though not of uniform distribution. On the lower aspect of the right frontal lobe the gyri were flattened, presumably due to enlargement of the anterior horn. The leptomeninges were not thickened. The vessels showed no definite changes. The cerebellum was of normal size and had normal gyri. Frontal section revealed spongy brain tissue with networks of varying size. The degeneration was most pronounced on the convexity and in the anterior two-thirds of the cerebrum there was atrophy of the gyri in the parieto-occipital lobes, but no polyporencephaly was observed. The ventricles were severely enlarged. The cystic necrotic processes had invaded the insula and the lateral areas of the corpus striatum in both sides. In the area of the thalamus, at the level of the massa intermedia bilateral atrophy was present in the upper median portions in the form of yellowish necrotic processes. Yellowish discoloration was not observed elsewhere. The remaining areas of the basal ganglia were sclerotic, with blurred outlines. The aqueduct and the fourth ventricle were not enlarged. There was slight granulation in the ependyma on the walls of the lateral ventricles and possibly also in the fourth ventricle. The cerebellum, pons and medulla oblongata were macroscopically normal on the sectioned surfaces.

Pathological diagnosis: pronounced polyporencephaly due to cerebral anoxia.

No. 14 (26001/203/1955)

A girl born in hospital on March 8, 1955 to a 30 year old primipara following normal pregnancy. The delivery was normal. BW was 3800 g. No asphyxia. Admitted to the DPGs on the second day because of convulsion and suspected intracranial haemorrhage. The convulsion did not recur, but she remained rigid, trembling and with a high-pitched cry until the 10th day. There was a cephalhaematoma in the right side. The eye movements are nystagmic, and ophthalmoscopy showed retinal haemorrhages. On discharge, 14 day later her condition was good, but follow-up was recommended.

Diagnosis: intracranial haemorrhage.

Re-examination at NPO of the RH at 3 months revealed spasticity in all four limbs, restlessness, tremor sensitivity to noise and a squint. Head circumference was normal at this time, but at about 2 years of age it was just below a crage, and when last seen at well over four years, it was well below the normal limit. At 9 to 10 months she has episodes of jerking in the legs, which did not recur however from her third month she was treated with phenobarbitone and myosiline. Her mental development was slow. At 4 years her speech comprehension was poor and she was able to make only a few sounds. Growth was good during the early months of life, but subsequently poor. Motor function was very defective; when seen last at four years she was unable to sit up alone.—There was no family history of cerebral disease.

Diagnosis: mental deficiency spastic quadriplegia, macrocephaly strabismus.

No. 15 (26262/3/1955)

A girl, born at term in a private clinic on March 11 1955 to a primipara, who after the first month of pregnancy had been operated on for corpus luteum cyst. Otherwise the pregnancy was normal. The prolonged delivery was stimulated by 13 or 14 injections because of lack of progress. The heart sound eventually became affected, and the infant was delivered by forceps. She was asphyxiated for an unknown length of time and was admitted to the DPGs during her second day of life because of convulsions and suspected intracranial haemorrhage. On admission she was rigid, restless and screaming, and during the second to fifth day she experienced numerous convulsions. There were also several episodes of harlequin colour change. The rigidity subsided within eight days. However her condition was described as unsatisfactory at discharge after 26 days, though no particulars were given. The outlook was considered doubtful.

Diagnosis: intracranial haemorrhage, nystagmus, strabismus.

Her development was severely retarded. At 7 months diagnosis of spastic quadriplegia was made on O.P. examination at the DPGs. Subsequently she was treated at other hospitals. She achieved no motor function and had hardly any contact with her surroundings. She could smile and frown, however. Her hearing was thought to be impaired and she did not talk. She was very restless. At about 18 months she experienced two episodes of convulsions and from the age of two, or two-and-a-half she exhibited repeated seizures.

EEG at 1 year 7 months showed an atypical pattern with absence of activity in central-parietal and central tracings in sleep as well as waking record. Frontal and temporal tracings revealed spikes, more pronounced on the left side.

MEG at the same age disclosed excessive enlargement of the lateral ventricles, the left being larger than the right. No cortical air was seen.

Her growth was poor and she had to be fed by tube most of the time. At about 18 months she was put under SA and at about 2 years she was placed in an institution (Karensinstitute), where she died of broncopneumonia some seven months later. There was no family history of cerebral disease.

Diagnosis: mental deficiency spastic quadriplegia, symptomatic epilepsy microcephaly

Brain section was performed by Dr Erna Christensen. The weight of the fixed

brain was 350 g. The cerebrum had been completely destroyed leaving a wall of only a few millimetres thickness, and the basal ganglia, which were atrophic. Brownish necrotic processes were observed laterally in the corpus striatum, otherwise no haemorrhage was seen. The cerebellum and brain stem were macro- and microscopically normal.

Pathological diagnosis: polyporencephaly due to cerebral anoxia.

No. 16 (5535/205/1955)

A boy born at term in a private clinic on June 10, 1955 to a grossly overweight primipara, who had exhibited oedema during pregnancy. Her blood pressure and urine were normal however. The delivery was induced and prolonged, and was accomplished by forceps with axis traction. There was no record of asphyxia, but the infant was given oxygen and lobeline immediately after birth and was referred to the DPGs without delay. On admission his condition was poor. He suffered several cyanotic attacks during the first day. He was restless, rigid and trembling, and there was grunting respiration. During the first few days there were repeated convulsions. His restlessness decreased after the fifth day but the rigidity and tremor lasted until the tenth day. He was discharged on the 15th day in apparently good condition, but our patient follow-up was recommended.

Diagnoses: intracranial haemorrhage, difficult birth.

He was readmitted when 2½ months old following vomiting and poor growth due to suspected pyloric stenosis. This diagnosis was not confirmed. He was markedly spastic, trembling, with a tendency to opisthotonus, and could neither focus nor smile. The diagnosis was spastic quadriplegia, suspected mental deficiency. The prognosis was considered to be grave.

PEG at 4 months revealed generalized pronounced enlargement of the ventricular system.

From this time on he suffered frequent clonic seizures and was given anti-convulsant therapy with some benefit.

EEG performed at 5 months showed severe abnormalities with generalized synchronous spikes and spike waves.

Head circumference at 6 months was lower borderline normal, and later on was clearly below even this limit. Motor as well as mental development was extremely retarded. At the age of 9 months he came under the care of SA and later was admitted to an institution (Andersvænge), where he died at the age of 2 years and 3 months.

There was no family history of cerebral disease.

Diagnoses: mental deficiency spastic quadriplegia, symptomatic epilepsy micro-encephaly

Brain section revealed microcephaly and microgyri, polyporencephaly especially cortical internal hydrocephalus, due to cerebral anoxia. The weight of the fixed brain was 500 g.

No. 17 (7116/205/1955)

A girl born at term in a private clinic on June 30, 1955. There was no record of age and parity of the mother nor of the pregnancy. The delivery was prolonged and was stimulated by repeated injections. Forceps with axial traction was applied. The infant was asphyxiated for 30 minutes, in the course of which 1/2 ml of coramine was given. She was immediately transferred to the DPGs in a desperate condition, flaccid, drowsy and showing no spontaneous movement. Subsequently she became restless, rigid and trembling. Over the first few days she sustained several cyanotic attacks with collapse. From the 8th day she recovered somewhat, however sucked and progressed poorly for 1½ months. At discharge, following 53 days' stay the outlook was considered doubtful.

Diagnosis: intracranial haemorrhage.

5 months later she was admitted to neurosurgical department (Blasbjerg Hospital). Following PEG studies, which revealed symmetrical enlargement of the ventricular system, diagnosis of cerebral atrophy following difficult birth, spastic quadriplegia, mental deficiency and microcephaly were made. She also suffered repeated clonic convulsions.

EEO was severely abnormal. No details are available, however. She was placed in a nursery where she died 1 1/2 years old. Post mortem was not carried out.

No facial cases of cerebral disease were elicited.

No. 18 (7653/355)

A girl, born in a private clinic at term on July 7 1955, to a 37-year old multipara, following pregnancy complicated by permanent nausea. The delivery was uncomplicated, but very quick. However the infant had the cord around its neck and was asphyxiated for a few minutes. Lobeline was given. Because of convulsions she was admitted to the DPGs during the first 24 hours of life, in extremely poor condition: flaccid, drowsy and cyanotic. She remained almost stuporous for the first week. Subsequently she became rigid. There were repeated cyanotic attacks during the first few days. Throughout the two months of her stay she suffered recurrent convulsions despite anti-convulsant therapy: the rigidity persisted and her growth was unsatisfactory.

Diagnosis: intracranial haemorrhage, cerebral palsy, symptomatic epilepsy.

She was readmitted at 6 months of age because of continued convulsions.

EEO 1) at six months was severely abnormal with frequent bursts of spikes with right-sided preponderance.

Her development was severely retarded and her growth remained poor. The previous diagnosis of spastic quadriplegia was supplemented by mental deficiency and microcephaly.

Her later development was extremely slow in all respects and she continued to exhibit tonic convulsions. She did not respond to noise and did not talk. At about 4 years she was admitted to the Dept. of Paediatrics of the RH.

EEO 2) at this time was again severely abnormal. Her sleep record as well as the waking record were characterized by spikes and spike waves of 2-3 per second, with changing laterality.

PEG revealed moderate enlargement of the lateral ventricles. The third ventricle was large owing to atrophy of the corpus callosum. There was considerable cortical atrophy.

At about 4 years she was placed under the care of S.A. She died 4 years 2 months old from bronchopneumonia.

Brain section by Dr Erna Christensen showed microcephaly and microgyri, predominantly in the cerebellum, dysplasia of the cerebrum due to perinatal anoxia, lateral hydrocephalus with dysgenesis of the corpus callosum and the septum pellucidum. No sclerotic abnormalities were seen, however, there were signs of partially arrested development during the perinatal period with degenerative changes in the form of gliosis, presumably due to anoxia.

There was no family history of cerebral disease.

No. 19 (443/3/1947)

A boy born at term in hospital on Aug. 11 1947 to an unmarried primipara following normal pregnancy. Normal delivery, no asphyxia. Admitted to the DPGs at 24 days because of convulsion on the previous day. On admission the infant was feeble and trembling, and during the first three days of admission he had several seizures. Lumbar puncture was performed, the spinal fluid was straw-coloured, but otherwise normal. Jerks, which had started on the second day of life, had subsided before admission. The temperature quickly fell to normal. There were no alterations of tone, but the eye movements were nystagmoid. The infant was discharged after 32 days in apparently good condition, though the nystagmus persisted.

Diagnosis: Intracranial haemorrhage.

The maternal grandparents, who cared for the child, took him to a doctor at the age of one year as they considered that he was backward. He was unable to sit and was quiet and rather listless. Vision and hearing were felt to be normal. The somatic development was satisfactory and the neurological examination was normal (OP RH).

He could sit up alone by the time he was 2 years old and walk alone by 2½. His motor pattern appeared normal. Up to the age of 3 years he was very placid, but for a number of years subsequently became unmanageable and destructive. From the age of 6 he was no longer destructive, but ran around aimlessly and would not occupy himself. His fosterparent (maternal grandparents) had never really accepted the child, and the mother had gone abroad. When just over 3 years of age he was put under the care of SA and at about 5 years he was placed in an institution (Ebbesgård). There he was examined at the age of 10½. His behaviour was as mentioned above. He did not talk and no contact could be made with him. Somatic development and neurological examination were normal.

There was no family history of cerebral disease. The father was said to have been very moody.

Diagnosis: Idiocy aphasia, previous motor retardation.

No. 20 (15527/3/1952)

A girl born before term at home on Dec. 11 1952, to a 33-year old *multipara* following an uncomplicated pregnancy and a normal delivery BW was 300 g. No asphyxia. Sucked poorly for the first seven days at home and on the seventh day suffered a severe cyanotic attack, as a result of which she was given coramine and admitted to the DPGs. On admission she was moderately jaundiced there was, however no bloodgroup-incompatibility between mother and child, and the jaundice gradually subsided. On the day of admission and the next day several quite severe cyanotic attacks were observed, but were not repeated. A lumbar puncture was done. The spinal fluid was yellow but otherwise normal. There were no changes of tone or respiration. She was discharged after 29 days, in apparently good condition.

Diagnosis: sequelae of intracranial haemorrhage.

When she was about 2 months old her parents suspected that her head was larger than normal. This was confirmed at examination at the age of 3 months. At 4 months she was admitted to the Dept. of Neurosurgery of the RH. Ventriculography was performed and revealed excessive enlargement of the ventricular system including the fourth ventricle, and a ventriculo-cisternotomy was carried out. Operation revealed a severe arachnoiditis.

Her motor development was negligible. She was never able to sit or stand and was generally helpless. No definite neurological signs were demonstrable. She was placed in an institution under the SA (Andersvænge) at 2½ years of age. She was placid smiled on contact, but she could not talk and displayed no other mental activity. Her vision and hearing seemed normal. Head circumference was far above the upper normal limit (78 cm), but did not increase until shortly before the age of 3 when her conditions deteriorated. She died at the age of 3 years 1 month after four days high temperature and an episode of severe convulsions. At that time her head circumference was 88 cm.—In early life, probably within the first year there had been a period of recurrent brief convulsions with raising of the arms—which, however had ceased spontaneously before admission to Andersvænge (infantile spasm?).

No family history of cerebral disorder was reported.

Diagnosis. Idiocy pronounced hydrocephalus, symptomatic epilepsy aphasia.

Brain section (Dr Erna Christensen) showed severe internal hydrocephalus due to an Arnold-Chiari syndrome, suppurative meningitis, most pronounced in the posterior fossa, occlusion of foramina Magendii et Luschka, incipient granular ependymitis. (The cerebrospinal fluid amounted to 4 l litres).

No. 21 (13399/3/1953)

A boy born at term in hospital (RH) on Oct. 8, 1953. The mother was a multipara, she had been subject to oedema and vomiting during the pregnancy. The delivery was preceded by feeble labour for 10 days; it lasted for 50 hours and was stimulated several times. Otherwise the course was normal. BW was 4100 g. No asphyxia. During the first few days the infant was flaccid, but later became rigid and restless. On the 12th day he was transferred to the DPOs, still somewhat rigid, and making poor progress. Hydrocephalus was suspected, as it had been at the RH. He also had right-sided pes equino-varus. When discharged 18 days later he was still moderately rigid.

Diagnosis: sequelae of prolonged delivery right-sided pes equino-varus.

The parents suspected delayed development shortly before the child was six months old, because of listlessness, lack of response and unsatisfactory growth. When 13 months old he was referred to the OP of the RH because of suspected hydrocephalus. His head circumference was obviously above the upper normal limit and he was severely retarded physically as well as mentally. He was transferred to the Dept. of Neurosurgery RH, where PEG was performed. This revealed enlargement of the lateral ventricles, more pronounced on the left side. The third ventricle was poorly filled, the fourth ventricle was in correct position. The radiological diagnosis was generalized cerebral atrophy—sequelae of birth trauma? Operation was not recommended. At the age of 18 months he was placed under the care of SA and shortly after admitted to an institution (Ebbesgård). He sat up alone at 2 years 9 months, walked at 3 years 9 months. His gait was affected by his foot deformity. Hand movements were normal. He was severely mentally defective; at the age of 3 years his DQ was 47 (according to Bühler-Hetzer). He was placid and cheerful, glad of company could play with simple toys. His head circumference was still above the upper normal limit, but had not increased further and the shape of his head was not markedly hydrocephalic. He had epicanthus and single horizontal palmar lines, but no other mongoloid features. His vision and hearing were felt to be normal, but he had a mild squint. He could say single words at about 5 years.

No family history of cerebral disease was elicited.

Diagnosis: incubated hydrocephalus, aphasia, strabismus, pes equino-varus.

N 22 (20451/3/1954)

A boy born at term in a private clinic on Jan. 12, 1954, to a multipara, who had nuptalgia and vomiting during the pregnancy. The delivery was induced due to a right low. The course was uncomplicated and the infant was not asphyxiated. He was somewhat restless during the first 24 hours, subsequently flaccid, and sucked poorly. He was therefore admitted to the DPOs on the 8th day. The flaccidity persisted and he continued to suck poorly but eventually his growth became normal. He was discharged after 13 days in apparently good condition.

Diagnosis: congenital debility

The parents first suspected that something was wrong when at the age of 2-3 months he was very restless and flaccid, and he was re-admitted for observation at 3 months. His muscle tone was difficult to judge, as were his vision and hearing. The tentative diagnosis was Little's disease.

He was able to stand up with help at one year, walked by the age of 2 years. He used his hands in a normal way. His growth was poor during his first two years, but subsequently became normal. His mental development was retarded, though specific testing was never carried out. On examination, at the age of 3 years, his development was estimated to correspond to the age of 1½ years. His speech was much retarded. At follow-up, when aged 4½ years, he was able to say only single words. His hearing was much impaired. He was examined at the National Centre for the Deaf, on the last occasion at about 4½ years. The diagnosis was bilateral neurodegenerative suspected aphasic disturbance. It was suggested that the peripheral

hearing loss was complicated by some other form of hearing defect of unknown aetiology. He was given a hearing-aid, but would not use it. His head circumference had always been high borderline normal, hence a PEG was performed at the age of 18 months, which revealed a mild internal hydrocephalus. At the same age angiocardiology revealed an asymptomatic cardiac malformation in the form of an abnormal entrance of the inferior vena cava. On follow-up he appeared mentally retarded his development was estimated as that of a 2 year old. He made himself understood quite well by means of gestures. Though somewhat clumsy no definite neurological abnormalities could be found. His vision was normal. His head circumference was just below the upper limit of normal.

There was no family history of cerebral disease.

Diagnoses: mental deficiency hypacusis (neurolabrynthopathy), suspected aphasia, motor retardation, mild hydrocephalus, (congenital heart disease).

No. 23 (18337/3/1934)

A boy born at home on Nov 19 1934 a little before term to a 33-year old primipara following a normal pregnancy. The delivery was uncomplicated, BW 3500 g. The infant was asphyxiated for 5 minutes, initially flaccid thereafter he became restless, rigid and sucked poorly. For that reason he was admitted to the DPGs on the 12th day. Here he remained restless, mildly rigid and sucked poorly. He was discharged after 20 days.

Diagnoses: congenital debility suspected cerebral palsy

The father had epilepsy though had been seizure-free for two years at the time of the patient's birth. The mother had migraine.

At the age of 6 weeks the boy was readmitted because of poor growth. He was found to be slightly rigid, trembled when he cried, and sucked poorly. The diagnosis was suspected cerebral palsy. His growth soon after became normal.

He was able to sit up alone at 10 months and walk alone at 2 years, though his gait was unsteady. At follow-up, when he was aged 4 years, he was still somewhat clumsy though he walked normally in spite of moderate knock knees and flat feet. Neurological examination was normal. His mental development was retarded his speech was severely defective, consisting of only a few words. However he seemed to have normal comprehension of speech and normal hearing. At 3 4 and 5 years he was seen at the State Institute for Speech Disorders with a view to speech therapy. However each time he was felt to be too immature. Aphasia was suspected.—When about 5 1/2 years old he was placed under the care of S.A. At this time his mental development was estimated to equal that of a 3-year-old.

He was seen repeatedly at the NPO, RH, where, at the age of 18 months, a mild paraplegia was suspected. The diagnosis was later modified, since no abnormalities of muscle tone or reflexes were demonstrable.

Final diagnoses: mental deficiency aphasia, motor retardation.

No. 24 (24248/3/1955)

A boy born at term at the RH on Feb. 2, 1953 to a 40-year-old primipara following a normal pregnancy. The delivery was normal however the membranes had ruptured 4 days prior to delivery. There was asphyxia for a few minutes. He was transferred within the first 24 hours to the DPGs suspected of hydrocephalus. During the first day of life he exhibited cyanotic attacks, rigidity and opisthotonus alternating with flaccidity. The latter persisted for a few days the other symptoms regressed after the first day. He was discharged after 20 days in apparently good condition. No evidence of hydrocephalus was found, though the head, on admission, showed pronounced moulding.

Diagnosis: intracranial haemorrhage

The parents suspected that the child's development was retarded when at 18 months he was unable to walk and continued to be restless. He sat up at the usual age of

6 months. At 2 years, having just begun to walk, he was examined by two neurologists, one of whom felt that the patient was "spastic" while the other did not. On follow-up, at the age of 4, he was somewhat clumsy, his gait rather broad-based and his running rather slow for his age; however, no abnormalities of muscle tone or reflexes were elicited. His hand movements were normal. He appeared somewhat mentally retarded and his speech was severely retarded consisting of only single words. His comprehension of speech was relatively good and he made himself understood by gestures. The somatic development was satisfactory. However his head circumference was clearly below the lower normal borderline.

At 4 years 3 months he was tested by a psychologist at the Dept. of Paediatrics of the RH, who found an IQ of 59 and the mental development compatible with his level of speech. On this occasion he was also seen by a speech therapist, who found lack of concentration and receptive weakness. At 5 years of age he was placed under S.A.

When 2 years old he experienced an episode of pallor and unconsciousness, probably accompanied by flaccidity. Similar episodes occurred at the age of 4 and 4 years 2 months. He was very sensitive to noise.

An EEG done at 4 years 3 months was normal. Repeat EEG at 5 years 1 month showed normal waking pattern, during sleep a spike focus was seen in the left temporo-frontal tracing.

There was no family history of cerebral disease.

Diagnosis: mental deficiency previous motor retardation, aphasia, symptomatic epilepsy microcephaly

No. 25 (7791/205/1955)

A boy born at home at term on July 7 1955, to a multipara following normal pregnancy. The delivery was not prolonged, however was stimulated by injections and terminated by episiotomy due to an abnormal heart sound. BW was 4500 g. The infant was asphyxiated for about 5 minutes. He was admitted to the DPGs on the second day with diagnosis of asphyxia and congenital heart disease following cyanotic attacks beginning on the first day of life. He was flaccid and restless and had several cyanotic attacks the next few days. From the third day onwards he was trembling and during the fourth to sixth day he had repeated convulsions. Thereafter the symptoms improved and he was discharged on the 20th day in apparently good condition. No evidence of heart defect had been detected.

Diagnosis: intracranial haemorrhage.

The parents suspected retarded development when the boy was 6-7 months old. He sat up alone at 9 months, walked alone at 2 years. At follow-up, when he was about 3½ years old, his gait seemed somewhat slow and too broad-based for his age, and he was unable to run. Otherwise his motor pattern was normal and he failed to exhibit any changes of muscle tone or reflexes. His height was 12 cm below average, but he was well-nourished and well-proportioned. However his head circumference was clearly below the lower normal borderline (48.5 cm). He had a convergent squint. His hearing and vision were felt to be within normal limits, but he was mentally retarded and conspicuously unresponsive. His mother complained that she never made visual contact with him. At home he was not interested in other people or toys and was very temperamental. His speech was characterized by repetitions. During his first year of life he had been seen at intervals at the OP clinic at the RH, but later appointments had not been kept. He was found to be retarded, but neurological examination was negative. At follow-up psychological examination was planned, but the parents were not interested. EEG was normal.

The diagnosis was mental deficiency suspected autism, previous motor retardation, microcephaly convergent strabismus.

At the age of 7 years he was seen again at the above clinic, as he had reached school age and his parents doubted that he could get on at a normal school. His

motor pattern was normal, but in stress-situations strange, stereotyped hand movements were observed. The neurological examination was normal. His development had been unsatisfactory. He showed lack of concentration and never played alone or with other children and had no real contact with anybody. He seemed to have great difficulty in orientation within as well as out of the home, and the mother felt that his vision was poor. His speech was quite good, but he was unable to carry on a conversation. He would often repeat questions when asked and he still reiterated words and sentences over and over. His hearing was thought to be good. Eye examination was negative apart from a squint. EEG was still normal. Psychological tests revealed an IQ (Binet) of 48. The distribution of correct answers indicated an organic factor with a predominance of perceptual disturbances. He was placed under the SA.

No family history of cerebral disease was elicited.

No. 26 (708/3/1948)

A girl born in a private clinic at term on Nov. 6, 1948, to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by injections; the presentation was anterior vertex. Forceps were used. The infant was asphyxiated for about five minutes, at first was flaccid and subsequently restless. On the second day she was admitted to the DPGs because of convulsions, the suspected diagnosis being rupture of the cerebellar tentorium. On admission she was restless and rigid during the second to fourth day there were repeated convulsions. The convulsions as well as the increased muscle tone were bilaterally equal. A transitory right sided facial nerve palsy was observed. The symptoms decreased and she was discharged after 16 days in apparently good condition. The diagnosis at discharge was intracranial haemorrhage.

When the child was about 4 months old her parents realized that she did not use the limbs on her left side to the same extent as those on the right. At 8 months she was admitted to the Dept. of Paediatrics at the RH where a diagnosis of left-sided spastic hemiplegia was made. She sat alone at 6 months, walked alone at 2 years. Mental development was normal. At follow-up, at well over 10 years of age, she exhibited a pronounced left-sided spastic paresis with atrophy of the limbs of the left side. Her somatic development otherwise was satisfactory. Mentally she appeared perfectly normal and had been able to attend a normal school. Her speech was normal.

There was no family history of cerebral disease.

Diagnosis: left-sided spastic hemiplegia.

No. 27 (12392/3/1951)

A girl born in hospital at term on Oct. 17 1951 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by repeated injections owing to weak labour. McIlwain's forceps were used. The BW was 4800 g. No asphyxia was reported. She was rather restless and sucked poorly. On the ninth day she suffered cyanotic attacks and convulsions and was admitted to the DPGs with a suspected intracranial lesion or congenital malformation. The cyanotic attacks and convulsions recurred from the ninth to the eleventh day; she was rigid and trembling. The symptoms abated and she was discharged after 15 days in apparently good condition.

The diagnosis, intracranial haemorrhage.

She walked alone at 18 months, but unsteadily and on her toes. At about 2 1/2 years she was seen by a neuropaediatrician at the Orthopaedic Hospital, who made a diagnosis of mild spastic paraplegia. Her head circumference was obviously above the upper normal limit, and hydrocephalus was suspected. Her speech was normal. Her mental development was also thought to be normal.

During her early years the patient experienced four episodes of chill, sweating and vomiting followed by sleep. At the age of 3 years she had an attack of unconsciousness, was started on anticonvulsant drugs and shortly thereafter admitted

to children's hospital (Queen Louise's Hospital). PEG was performed, revealing moderate dilatation of the left lateral ventricle, while the right was normal. When she had been seizure-free for a period of three years, the treatment was discontinued, the seizures recurred, however and the anticonvulsant therapy was reinstituted.

The following EEG-records were made: 1) at 3 years: no definite abnormalities, 2) at 3½ years: abnormal, with mild, generalized dysrhythmia in the form of slow activity for the age; spikes in the left hemisphere, 3) at 4 years: periods of normal activity less slow potentials, spikes persisting, 4) at 6 years 9 months: less abnormal.

At follow-up, when 6½ years old, the patient appeared mentally normal. She had speech and good gait. Her speech was normal; so were her hand movements. The legs were mildly spastic. Her head circumference was clearly above the upper normal limit.

There was no family history of cerebral disease.

Diagnosis: mild spastic paraplegia, mild internal hydrocephalus, symptomatic epilepsy strabismus.

N. 28 (7736/3/1953)

A boy born at term in private clinic on July 29 1953 to a primipara following normal pregnancy. The delivery was stimulated by repeated myoclonic cephalopelvic disproportion was suspected. Forceps with axial traction were applied. Asphyxia was not observed. The infant was transferred to the DPGs shortly after delivery because of cyanotic attacks and a haematoma in the right parietal region. He was restless, had episodes of apnoea and one convulsion within the first 24 hours. The next days he was restless, but otherwise normal. A skull fracture was demonstrated. He was discharged on the 23rd day in apparently good condition, follow-up was recommended, however.

Diagnosis: skull fracture due to birth injury suspected intracranial haemorrhage.

The parents suspected that something was wrong, when at 3-4 months the child did not smile and appeared flaccid. He was therefore readmitted at 6 months and was found to be physically retarded and rather flaccid. PEG revealed no abnormalities.

The diagnosis: mild case of Little's disease.

At the age of 7 months he was examined by neuropaediatrician at the Orthopaedic Hospital. No alteration of tone was demonstrable, but a mild disturbance of coordination was suspected. The diagnosis was cerebral palsy?, sequelae of intracranial haemorrhage? The prognosis was considered excellent.

His motor development was very slow during the first two years of life. At about 2 years, however accelerated, he learned, in rapid sequence, sitting and walking, but his balance was poor and he had difficulty in controlling head movements. His mental development was considered satisfactory. At about 2 years of age he said single words and at three he was able to form sentences, though with faulty pronunciation. At the age of 4 years his hearing was found to be defective. Focusing had always been difficult; his vision was thought to be normal, however. At follow-up, at the age of 5 his motor pattern was still characterized by defective coordination, his gait was unsteady and he was unable to run. Fine movements of the fingers were impaired. The muscle tone was variable, often slightly increased. The somatic development otherwise was satisfactory. His speech was characterized by faulty articulation and mild stammering. He was able to focus briefly and had mild convergent strabismus. Mentally he appeared essentially normal.

Familial cases: none.

Diagnosis: ataxia, impaired hearing, impaired articulation, convergent strabismus.

N. 29 (4430 3/1954)

A boy born at term at home on May 29 1954, to primipara following a normal pregnancy. The delivery was prolonged, but apparently normal. BW was 3210 g. The infant was asphyxiated for few minutes, for which artificial respiration as well as nakebamide and alternating hot and cold baths are given. He was immediately ad-

motor pattern was normal, but in stress-situations strange, stereotyped hand movements were observed. The neurological examination was normal. His development had been unsatisfactory. He showed lack of concentration and never played alone or with other children and had no real contact with anybody. He seemed to have great difficulty in orientation within as well as out of the home, and the mother felt that his vision was poor. His speech was quite good, but he was unable to carry on a conversation. He would often repeat questions when asked and he still reiterated words and sentences over and over. His hearing was thought to be good. Eye examination was negative apart from a squint. EEG was still normal. Psychological tests revealed an IQ (Binet) of 48. The distribution of correct answers indicated an organic factor with a predominance of perceptual disturbances. He was placed under the SA.

No family history of cerebral disease was elicited.

No 26 (708/3/1948)

A girl born in a private clinic at term on Nov. 6, 1948 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by injections; the presentation was anterior vertex. Forceps were used. The infant was asphyxiated for about five minutes, at first was flaccid and subsequently restless. On the second day she was admitted to the DPGs because of convulsions, the suspected diagnosis being rupture of the cerebellar tentorium. On admission she was restless and rigid during the second to fourth day there were repeated convulsions. The convulsions as well as the increased muscle tone were bilaterally equal. A transitory right sided facial nerve palsy was observed. The symptoms decreased and she was discharged after 16 days in apparently good condition. The diagnosis at discharge was intracranial haemorrhage.

When the child was about 4 months old her parents realized that she did not use the limbs on her left side to the same extent as those on the right. At 8 months she was admitted to the Dept. of Paediatrics at the RH where a diagnosis of left sided spastic hemiplegia was made. She sat alone at 6 months, walked alone at 2 years. Mental development was normal. At follow up, at well over 10 years of age, she exhibited a pronounced left sided spastic paresis with atrophy of the limbs of the left side. Her somatic development otherwise was satisfactory. Mentally she appeared perfectly normal and had been able to attend a normal school. Her speech was normal.

There was no family history of cerebral disease.

Diagnosis: left-sided spastic hemiplegia.

No 27 (12392/3/1951)

A girl born in hospital at term on Oct. 17, 1951 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by repeated injections owing to weak labour. Kielland's forceps were used. The BW was 4800 g. No asphyxia was reported. She was rather restless and sucked poorly. On the ninth day she suffered cyanotic attacks and convulsions and was admitted to the DPGs with a suspected intracranial lesion or congenital malformation. The cyanotic attacks and convulsions recurred from the ninth to the eleventh day she was rigid and trembling. The symptoms abated and she was discharged after 15 days in apparently good condition.

The diagnosis: intracranial haemorrhage.

She walked alone at 18 months, but unsteadily and on her toes. At about 2 1/2 years she was seen by a neuropaediatrician at the Orthopaedic Hospital, who made a diagnosis of mild spastic paraplegia. Her head circumference was obviously above the upper normal limit, and hydrocephalus was suspected. Her speech was normal, her mental development was also thought to be normal.

During her early years the patient experienced four episodes of chill, sweating and vomiting followed by sleep. At the age of 3 years she had an attack of unconsciousness, was started on anticonvulsant drugs and shortly thereafter admitted

Polidine was also given twice. The infant was asphyxiated for a few minutes. She was admitted to the DPGs within the first 24 hours because of grunting respiration, the diagnosis of suspected intracranial haemorrhage. She recovered rapidly and was discharged 2 days later.

Diagnosis: congenital debility

She sat alone at 8 months and walked alone at 16 months. There were no motor problems. Her mental development was satisfactory. She talked intelligibly at 2 years, and her hearing was normal.

She had no convulsions, though within the first three years of life she suffered some brief spells of unconsciousness.

She was followed-up at about 3½ years of age. Clinical and neurological examination was normal except for a slight, non-familial divergent strabismus.

An EEG carried out when she was under 6 years old was mildly abnormal with dominant frequency of 8 per second and a few small spikes in the right frontal region. During photic stimulation small spikes were also seen in right parietal region. Hyperventilation did not precipitate specific changes. During sleep small spikes on the right side were again seen, though less pronounced. The record was indicative of epilepsy.

Diagnosis: fainting spells in the past, suspected epilepsy, divergent strabismus.

No. 37 (620/3/1948)

A boy born at term at home on Oct. 10, 1948, to multipara, following normal pregnancy. The membranes were thought to have ruptured one month prior to delivery.

He was stimulated by injections. Morphine was not given. The infant was not asphyxiated, but was admitted to the DPGs during the first 24 hours because of cyanotic attacks. On admission he was cold, somewhat flaccid, and respiration was grunting. He recovered quickly, however he sucked poorly for the first five days. This feature improved somewhat, but his growth was unsatisfactory throughout the first month. Otherwise his condition was normal, and he was discharged after 35 days in apparently good condition. Follow-up was recommended.

Diagnosis: congenital debility

His subsequent growth and motor development were normal. He walked alone at one year. His visual acuity was somewhat diminished due to left-sided cataract (senilis). He talked at 18 months. His hearing was normal.

At the age of 4 years he was admitted to Blegdamshospitalet with a diagnosis of sequelae of meningitis and meningioma. He was treated with penicillin and discharged after one week. The spinal fluid was normal.

His mental development had been fairly normal. He started school at the usual time, but had to repeat the second grade. Subsequently he did well. He had always been hyperactive and aggressive, and his attention span was short. He did not get on well with his companions or older siblings.

There was no history of convulsions, but nocturnal enuresis was present until the age of 10 years at least.

At follow-up, at the age of 10 years, his physical development was in line with his age. He was somewhat obese. His mental development was also compatible with his age, but during the examination he appeared rather restless. The neurological examination was normal. An EEG was performed, revealing severe dysrhythmia with a number of generalized synchronous paroxysms of low frequency (3-4 per second) and spikes, with preponderance in the frontal-temporal tracing.

One year after this examination the patient was reported to have suffered two episodes of unconsciousness, during which he banged his head on the floor. Convulsions were not observed. He was given antiepileptic drugs and subsequently followed-up at the NPO at the RH. During the next four years he exhibited recurrent fainting spells at varying intervals. Difficulty in concentration and with his behaviour at school persisted, and later on he had trouble keeping his job. EEG improved quickly and

mitted to the DPGs with a diagnosis of asphyxia. His condition was poor he was found to be weak, drowsy flaccid with peripheral cyanosis. Later he trembled and jerked, and this persisted to some extent on discharge 19 days later. His growth was poor during the first two weeks, after which it improved.

Diagnosis: sequelae of difficult delivery

He was seen as an outpatient at the age of one month, at which time his growth was satisfactory he smiled and focused, but he had a mild squint he seemed to move his limbs normally but was still somewhat trembling and jerking. The patient was not followed-up, but his condition has been described in a report from the Orthopaedic Hospital at Aarhus, where he had been seen because of a diagnosis of mild spastic paraplegia since the age of three years. His motor development had not been retarded he started to walk at 13 months; his gait had however been impaired by poor balance. His upper limbs had always appeared normal. Earlier examinations had revealed a mild increase in muscle tone and reflexes in the lower limbs and a bilateral Babinski reflex. These findings became less pronounced over the years, and at six his gait was essentially normal. His mental and somatic development as well as his speech had been satisfactory at all times.

There was no family history of cerebral disease.

Diagnosis: mild spastic paraplegia, strabismus.

No 30 (757/3/1952)

A girl born at home at term on April 14 1952, to a multipara following an uncomplicated pregnancy. The otherwise normal delivery was stimulated by injections. No asphyxia was reported but coramine was given. Shortly after birth she was admitted to the DPGs with a diagnosis of congenital heart disease. On admission she was almost moribund cyanosed and flaccid with laboured respiration however she recovered within the first 24 hours and was discharged 4 days later in apparently good condition. There were no signs of heart defect.

Diagnosis: congenital debility

Information on subsequent development was unobtainable. After repeated requests she appeared at the follow-up accompanied by her grandmother who did not know anything about her past history.

A discharge summary from the Dept. of Neurology at the RH where the child had been seen as an out patient, revealed that, since the age of 18 months, the child had exhibited episodes of flaccidity drowsiness, upward movements of the eyes and cyanosis of the lips lasting for about one minute and followed by deep sleep. The frequency of these episodes was not recorded. She was first examined at the age of 5 years because of these attacks. EEG was moderately abnormal and indicative of epilepsy with large spikes posteriorly towards the midline. Anticonvulsant therapy was instituted the frequency of the attacks diminished, their type changed, and one year later was described as psychomotor epilepsy. The last EEG at the age of 6½ was still markedly abnormal the abnormalities were generalized, but with a preponderance to the left, however. The diagnosis was epilepsy suspected atrophic encephalopathy due to neonatal asoxia.—She had nocturnal enuresis. Neither epilepsy nor enuresis were familial. She was said to be hyperactive, and it was felt that she would not be ready for school until the age of 8.

At follow-up, when the patient was well over 6½ years, the only abnormal finding was a convergent squint. Physical development was in line with her age and she appeared sensible, intellectually possibly low borderline for her age. Her speech and motor pattern were normal. Neurological examination was normal, and there were no signs of heart disease.

Diagnosis: epilepsy mental retardation? nocturnal enuresis, convergent strabismus.

No 31 (11172/3/1953)

A girl born at term in a private clinic on Sept. 17 1953 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by repeated injections.

tally on his own. When addressed in a loud voice, he could be brought out of the attack. At 18 months of age he was readmitted to the DPGs following a generalized tonic seizure of a few minutes' duration, associated with fever. The examination was normal, except for a rash.

Diagnosis: exanthema subitum, febrile convulsions.

An EEG as recorded at age two years, showing no abnormalities. He was seen at follow-up at the age of 3, at which time he had developed according to his age, physically as well as mentally. The neurological examination was normal.

Diagnosis: febrile convulsions, suspected epilepsy

Ac. 33 (15152/3/1952)

A boy born at a private clinic, shortly before term, on Dec. 9 1952, to primipara, following a normal pregnancy. The delivery was prolonged. There is no record of the use of labour stimulation or morphia. Apart from breech presentation the delivery was uncomplicated. BW was 2400 g. The infant was not asphyxiated and was essentially normal for the first two days. However on the third day he developed cyanotic attacks and convulsions. He was admitted to the DPGs and on that day had one more seizure. He was restless and irritable for the first three days, but exhibited no symptoms during the rest of his stay and was discharged after 21 days in apparently good condition.

Diagnosis: sequelae of intracranial haemorrhage?

His growth was poor during the first year of life, then improved, even though he was somewhat undernourished. His motor development was slow: he could not sit up until the age of 14 months or walk until about 20 months. At 8 months he was readmitted to the DPGs where ophthalmopathy and spasticity were suspected due to delayed development. Because of strabismus and nystagmus he was transferred to the Dept. of Ophthalmology. Ophthalmoscopy revealed no abnormalities. However it gradually became evident that the visual acuity was poor in both eyes, mainly in the left side. He underwent surgery for his squint at the age of 2 years and the following year was provided with glasses.

His pattern of movement was very unsteady to begin with, but improved considerably after he began to wear glasses. He was left-handed (not familial). From the age of 2-4 years he had two episodes of convulsion precipitated by temper tantrums. Until the age of 5 he would frequently grind his teeth at night. His mental development was satisfactory with no behaviour disorders. It was anticipated that he would be ready for school at the usual time. His hearing was normal and he talked by the time he was 2 years old.

He was well over 6 years old at the time of follow-up. His height was 7 cm below average; however he was well-proportioned and well nourished. His mental development appeared to match his age. His speech was normal. He wore glasses and had patch over the left eye. With the use of glasses his motor pattern including fine co-ordinated movements was normal. Without glasses there was unsteadiness and there was obvious impairment of vision in both eyes. He preferred to use his left hand, though he had no trouble using his right hand. No neurological abnormalities were seen.

EEG at 7 years 3 months was normal.

Diagnosis: previous motor retardation, latent amblyopia, convergent strabismus, breath-holding spells, previous poor growth.

Ac. 36 (178/3/1946)

A boy born at private clinic before term on June 10, 1946 to a 27-year-old multipara following normal pregnancy. The delivery was uncomplicated and not stimulated, no morphia was given. BW was 2150 g. The infant was cyanosed, but not asphyxiated at birth. Since he suckled poorly and had cyanotic attacks in association with feeding he was transferred to the DPGs aged one week. On admission he was jaundiced, but jaundice subsided within a few days, and he presented no other abnormal features.

during the following four years the records were normal or only mildly abnormal; during the next two years they remained quite normal. There were no convulsions during this period. The antiepileptic drugs were therefore discontinued, and he remained seizure free as far as information is available i.e. for the next 6 months.

In 1960 at the age of 12, he was examined by a psychologist, who reported that the boy was normal to bright, but had difficulty meeting the demands made by himself and by others because of lack of development of the finer cerebral functions in relation to language: an inability to put his thoughts together to take in and comprehend did not match his technical reading ability and the extent of his vocabulary. These features in a boy with epileptic symptoms would be regarded as manifestations of organic immaturity of the mild receptive-aphasia type.

Diagnosis: symptomatic epilepsy, behaviour difficulties, enuresis, cataract of the left eye (familial).

No 33 (23947/205/1955)

A boy born in a private clinic at term on Feb 9 1955 to a primipara following a normal pregnancy. Delivery was uncomplicated, not induced and morphia was not given. The infant was not asphyxiated and exhibited no symptoms during the first days apart from some flaccidity. On the fourth day he developed harlequin colour change and sucked poorly and he was admitted to the DPGs with a diagnosis of asphyxia. On admission he was flaccid and cold. The next day he had 2 episodes of left-sided convulsions, however recovered within a few days and had no further seizures. On the 13th day he was discharged in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth was normal. Motor development was good, though he could not sit up until he was 8 months or walk until 16 months. His motor pattern was normal however he was left handed (non-familial). His mental development was satisfactory and he presented no behaviour problems. There was a squint, but his vision was felt to be normal. His hearing and speech were also normal. From the age of 13 months onwards he sustained 8 to 10 episodes of generalized clonic convulsions, all associated with fever. The length of the episodes increased from between 5 and 10 to 45 minutes and were followed by sleep. The last episode occurred at the age of 3 years. No treatment was given. Familial history of convulsions was not reported.

At follow up he was 3 years 9 months old. Physical and mental development were in line with his age. The neurological examination was normal. He preferred using his left hand, but was able to use his right hand well (i.e. when eating). There was an intermittent squint.

EEG was normal.

Diagnosis: febrile convulsions, suspected epilepsy, convergent squint, left handedness.

No 34 (20598/55)

A boy born at term in a private clinic on Dec. 13, 1955 to a primipara, following a normal pregnancy. The delivery was uncomplicated and not induced. Pethidine was given once. The infant had the cord around the neck once, but was not asphyxiated. Because of cyanotic attacks he was admitted to the DPGs within the first 24 hours, suspected of a congenital heart disease and aspiration to the lungs. On admission his respiration was grunting, and he exhibited repeated cyanotic attacks during the first day. His respiration was quickly corrected, and no abnormal features were apparent for the rest of his five days stay. The examination revealed no evidence of heart disease.

Diagnosis: congenital debility.

His growth and development were normal. He walked alone by one year and talked before he was two. His vision and hearing were normal so was his behavioural pattern. From the age of one year he exhibited daily episodes of drowsiness accompanied by staring and jerking of the arms, most frequent when he was playing peace-

Diagnosis: behaviour disorder convergent strabismus, amblyopia of the right eye, impaired hearing of the right ear (*postinfectious*), speech retardation, previous dysplasia.

No. 38 (23/3/1946)

A girl born in a private clinic before term on April 10, 1946, to a 29-year-old multipara following an uncomplicated pregnancy. The delivery was normal, no labour stimulation or morphine were given. BW was 1440 g. The infant was asphyxiated for 10 minutes and was given oxygen and artificial respiration and was transferred to the DPGs. During the first few days she suffered repeated cyanotic attacks, but was otherwise normal apart from poor growth. She stayed in hospital for 12 days and was discharged in apparently good condition.

Diagnosis: prematurity congenital debility

Her growth was slow for the first 6 months, then improved. The motor development was rather slow she did not sit up until rather late and did not walk until 22 months. Her motor pattern was normal. At a little over 2 years squint was noted, both was treated surgically at the age of 5. The mental development was satisfactory. However the parents recognized that something was wrong when at 4 or 5 years she still did not speak properly. At 6½ years she entered the State Institute for Speech Disorders, where a hearing loss, mainly of high frequencies, was revealed. She had trouble with her articulation of consonant combinations. A year later she started in a special class for children with hearing and speech defects at municipal school; she did fairly well and her speech improved. There was no change in her deafness. She got on quite well with other children, even though she was rather introvert and sensitive.

There was no family history of hearing loss.

At follow-up, aged 12, she was physically developed according to her age. Neurological examination and EEG-record were normal. She appeared mentally normal during the examination. She still had slight trouble with the pronunciation of s, t, k and g.

Diagnosis: hearing defect, dysphasia, operated squint, previous poor growth, previous retardation of motor development.

No. 39 (16/2/1947)

A boy born at home before term on May 9 1947 to a 36-year-old primipara following an uncomplicated pregnancy. The delivery was normal. Labour stimulation was not applied, but one analgesic injection was given. BW was 1350 g. The infant was asphyxiated for a few minutes and was immediately admitted to the obstetric dept. of the R.H. 13 days old he was transferred to the DPGs. His condition was quite good during the first few days of life, but after the fourth day he had to have oxygen intermittently due to cyanotic attacks. From the 24th day he was free from attacks. No other symptoms were observed. His growth was poor for the first two weeks, then improved. He stayed in hospital for 58 days and was discharged in apparently good condition.

Diagnosis: prematurity congenital debility

Subsequently his growth and development were satisfactory. He walked alone at 15 months and his motor pattern was normal. He began to talk rather late at 3-4 years he said only single words, and when, at 6 years, he still did not talk properly he was given speech therapy for one year. He started school at the usual time. At school he had to have special lessons in reading for one year and he was referred to the National Centre for the Deaf. The examination revealed bilateral nerve deafness, due to premature birth. His hearing loss affected only high frequencies. He was given hearing aid, which he used at school. There was family history of deafness.

He offered no behaviour problems.

On follow-up examination, at 11 years, he was found to be normally developed,

apart from poor growth for the following 2 months. He was discharged after 152 days in apparently good condition.

Diagnosis: congenital debility

His development had been essentially normal. He walked rather late (18 months); however his motor pattern was quite normal. He started to talk before he was 2 years old, but did not speak properly until he was well over 6. He was therefore given speech therapy and within 3 months his speech was normal. Hearing and vision was normal. His mental development as regards learning was satisfactory. He started school at the usual time and did well. IQ (Binet) at 6 years was 112. His behaviour was characterized by restlessness, a violent temper and lack of concentration, for which reason he was admitted to a children's hospital (Queen Louise's Hospital) at the age of 6 and 8 years. The diagnoses were neurosis, environmental stress and dysphasia. The history revealed a good deal of "sibling jealousy" but otherwise no real precipitating environmental factors. EEG showed mild generalized dysrhythmia. The dominant frequency was 7-9 per sec. Both occipital and central leads showed at several points single potentials of 4-5/msec. During hyperventilation a strong build up of slow potentials was seen the record soon became normal, however—He had never exhibited any epileptic manifestations and no special treatment was given. His behaviour difficulties gradually subsided. Nocturnal enuresis was present until the age of 9 years.

There was no family history of enuresis, speech defect or epilepsy

At follow-up, when he was about 12 years old, the boy was found to be somatically and mentally developed in line with his age. There were no complaints of behaviour problems, and on examination he appeared placid and sensible. The neurological examination was normal.

Diagnosis: behaviour disorder cerebral dysrhythmia, previous dysphasia.

No. 37 (253/3/1950)

A boy born in hospital (St. Lukas Stiftelsen) before term on June 7 1950, to a 39-year old multipara, following a normal pregnancy during which she had felt very tired. The delivery was very quick. No drugs were given. BW was 2000 g. Asphyxia is not reported, though nitethamide was administered. The infant was immediately transferred to the DPGs with a diagnosis of prematurity. He was rather flaccid on admission and sustained cyanotic attacks during the first 24 hours. His growth was unsatisfactory for the first two weeks, then improved, and his condition was essentially normal when he was discharged after 33 days.

Diagnosis: prematurity congenital debility

Growth was unsatisfactory for the first 6 years of life. During those years he suffered repeated infections of the upper respiratory tract. Following adenotonsillectomy at the age of 6 the infections ceased and his growth improved. His motor development was good: he sat up at 7 months and walked at one year; the motor pattern was normal. During his early years his hearing was thought to be normal. At the age of 7 a right-sided hearing loss was recognized, affecting high frequency sounds only and possibly caused by the previous middle ear infections. He had a convergent strabismus and was given glasses and an occlusive eyepatch. Visual acuity in the right eye was found to be diminished. His speech was retarded: he began saying single words at the age of 2. He stammered until the age of 4-5 and even after the age of 5-6 years his speech was only fair with imperfect articulation of certain consonants.

His mental development was fair. However his behaviour was characterized by restlessness and aggression. At the age of one and again at 2 years he was admitted to the DPGs with a diagnosis of neurosis, which was ascribed to environmental factors. He started school at 7 and did well.

At follow-up he was 8 years old, of about medium height, and obese. He had a convergent squint and wore glasses. His mental development was felt to be according to age, though possibly low borderline. His speech was normal. The neurological examination was normal. EEG was normal.

evoked aphasia, mainly of the expressive type. His intelligence could not be assessed exactly. He was placed in a group of patients with perceptive deafness and aphasia, where he made satisfactory progress after initial serious difficulties of adjustment. At the age of 8 he was again psychologically tested. His I.A. was found, with reservation, to equal 6½ years. The evaluation of his hearing had also been difficult. At the age of 8½ audiometry carried out at the National Hearing Centre revealed normal hearing. He was, nevertheless, provided with a hearing-aid, which it was anticipated would improve comprehension. As this was not the case, the hearing-aid was abandoned after 6 months. Following two years of therapy at the Institute for Speech Disorders he was transferred to the Institute for Dyslexia, which he attended a least until the autumn of 1966. He had great difficulties in talking as well as reading, though he worked hard and enjoyed the training.

His behaviour was satisfactory though less so than previously: he was extremely sensitive and irritable with other children. He had nocturnal enuresis until age 11 (Not treated).

He was 8½ years old at follow-up. Somatically he had developed in line with his age, his motor pattern was normal. Neurological examination was normal. Mentally he appeared babylike and clinging. His speech was defective and his articulation was poor. His comprehension of language was felt to be much improved. An EEG was recommended, but he did not attend at the appointed time.

Diagnosis: Aphasia, mainly expressive; mental retardation, previous motor retardation, previous enuresis, previous poor growth.

No. 42 (1923/3/1951)

A boy born at term on March 11 1951 to a 32-year-old multipara following normal pregnancy. Delivery took place in a private clinic and was induced for unknown reasons. During the delivery which was otherwise normal, morphia was given. The infant exhibited asphyxia for a few minutes, during which artificial respiration and cortisone 0.4 ml were given. Within the first 24 hours the infant was referred to the DPGs with diagnosis of prematurity. On admission his respiration was grunting; otherwise his condition was normal. Oxygen was given intermittently for the first six days. During the first 5 days he exhibited cyanotic attacks whenever gradual discontinuation of oxygen was attempted. After a few days his breathing became normal. After the 5th day he appeared normal except for poor growth, which persisted for two weeks. He was discharged after 23 days in apparently good condition.

Diagnosis: congenital debility

His later growth was good. His physical and mental development were normal apart from marked resilience and sensitivity to noise, mainly in the first 2 years. His vision and hearing were felt to be normal. He first began to talk at about 3 years of age, he said a few single words only and did not form sentences until the age of 5-6 years. He had mispronunciations of certain consonants, which did not justify speech therapy.

At follow-up when he was 7 years old, he was found to have developed in line with his age physically as well as mentally. He appeared placid during the examination. There was mispronunciation of h and r. Neurological examination was normal. He was referred for EEG, which was, however postponed until he was 8½ years old and showed a normal record. At this time he had started school, he did well, and his speech was normal.

Diagnosis: mild dysphasia, previous hyperactivity

No. 43 (9900 3 1952)

A boy born in hospital (St. Lukas Stiftelsen) at term on Sept. 16, 1952, to primipara of 30 years. The delivery was prolonged, stimulating injections were given and forceps were applied. There is no record of morphia. BW 4000 g. The infant was not asphyxiated, though was rather flaccid at birth and subsequently restless. On the

mentally as well as somatically. The neurological examination was negative. EEG was normal. There were a few mispronunciations—he had difficulty with t and k.—One year later speech therapy was repeated with good results. His progress in school was excellent.

Diagnosis: hearing defect, dysphasia.

No. 40 (1126/3/1949)

A boy born in hospital (Diakonissestiftelsen) at term on Feb. 10, 1949 to a 33-year-old primipara following an uncomplicated pregnancy. The delivery was prolonged. Labour stimulating drugs were given no information available about morphia. Forceps were used. No record of asphyxia. The infant was flaccid and sucked poorly and on the 13th day after developing a fever was transferred to the DPGs with suspected pneumonia. There his respiration was found to be normal, and examination of the lungs showed no abnormalities. The fever subsided within 3 days, he was still somewhat flaccid and sucked poorly during the following week, but then improved. He was discharged 14 days after admission in apparently good condition.

Diagnosis: intracranial haemorrhage.

His later growth was normal. So was his motor development, although he did not walk until he was 18 months. His mental development was good he started school at the usual time and did well. He presented no behavioural problems. There was enuresis until the 7th year (not familial). He began to talk at the "usual" time, but with a few mispronunciations, mainly of l, g and d. From the age of four impaired hearing was suspected. At 7 years he was taken to the Hearing Centre at Odense, where the diagnosis was bilateral congenital neurolabyrinthopathy (birth injury), high tone loss. He was given a hearing-aid, which he used with great benefit. On follow-up examination at the Hearing Centre one year later the findings were unchanged on the left side, but audiometry revealed progression of the defect on the right side.—There were no cases of deafness or speech defect in the family.

At follow-up the child, now well over 10 years old, was found to be normally developed, mentally as well as physically. The neurological examination was normal, the speech was normal. He still used a hearing-aid. EEG was not performed.

Diagnosis: bilateral congenital neurolabyrinthopathy previous mild dysphasia, previous enuresis.

No. 41 (91/3/1950)

A boy born at home at term on April 24, 1950, to a 31-year-old multipara following a normal pregnancy. There is no record of delivery complications or the use of morphia. Labour stimulating injections were given. Asphyxia is not mentioned. The infant was admitted to the DPGs on the first day because of cyanotic attacks. On admission he was rigid and somewhat trembling. No cyanosis was observed after the first day. The rigidity subsided after a few days he improved and was discharged after 8 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth was poor for the first 6 months, then improved. His motor development was at first retarded—he could not sit up until one year old, but walked at 15 months, and his motor pattern was normal. At 3 years of age he was referred to the Finzen Institute suspected of retarded mental development. However because of poor co-operation and a pronounced speech defect his intelligence could not be assessed. This was also true half a year later when he was admitted to the DPGs because of pneumonia. His speech was still defective, he said only single and imperfectly articulated words. However he did seem to have a better comprehension of spoken words. He received no special speech training and, in spite of earlier referral, was not tested until 7 years of age, when he was seen by a school psychologist. Proper testing was again impossible: he was, however assessed as backward or feeble-minded, and referral to the Institute for Speech Disorders was recommended. The examination

nation he was flaccid and cyanosed and his respiration was grunting. Cyanotic attacks are limited to the first 24 hours and respiration and muscle tone were restored to normal within a few days. Thereafter he exhibited no symptoms and was discharged after 14 days in apparently good condition.

Diagnosis: congenital debility

His growth and motor development were satisfactory he sat up at 7 months and walked at 15-16 months. His motor pattern was normal. Mental retardation was not observed. He began to talk at 3 years, with certain consonant defects.

There was family history of delay in talking.

At follow-up, when he was 8½ years old, his speech was still faulty he had trouble with the articulation of k, g and s. The physical and neurological examination was normal. His vision and hearing were felt to be normal. His mental development was considered normal for his age.

An EEG was recommended, but the parents refused.

Diagnosis: retardation of speech, mild dysphasia.

A 46 (7156/2/1953)

A boy born at term in private clinic on July 21 1953, to a multipara following normal pregnancy. The delivery which was uncomplicated, was stimulated by injection, and morphine was given. The infant was not asphyxiated and appeared normal for the first 24 hours except for a certain flaccidity. On the second day he was, however, admitted to the DPGs because of cyanotic attacks with diagnosis of suspected debility. On admission he was somewhat flaccid and trembling with grunting respiration. During the next 4 days he had repeated cyanotic attacks with decreasing frequency. His breathing became normal within a couple of days, and his trembling subsided. He was treated with oxygen for four days and was discharged on the sixth day in apparently good condition.

Diagnosis: congenital debility

His growth as well as motor and mental development were satisfactory. He was able to walk before the age of one year and his motor pattern was normal. His vision and hearing were also normal. He started saying single words at an early age. However he was unable to form sentences until he was 4½ years old, and his pronunciation was faulty. His behaviour had always been rather aggressive.

At follow-up, when he was 5 years old, his physical development was considered to be normal for his age. He was thought to be somewhat backward, but his behaviour appeared normal during the examination. Several consonants were mispronounced. The neurological examination was normal. An EEG was normal. He was referred to

speech therapist, who found imperfect pronunciation of consonants and a few grammatical errors. His diagnoses were speech retardation; expressive and, probably mild receptive aphasia. The child was referred to the Institute for Speech Disorders at the age of 6 years. At this time psychological testing was carried out, revealing an IQ of 101. His ability to concentrate was good. On Bender-Goldstein tests slight visuo-motor defects suggesting organic cerebral damage were demonstrated.

Diagnosis: speech retardation, expressive (and possibly receptive) aphasia.

A 47 (20335/3/1954)

A girl born at home at term on Jan. 21 1954, to a primipara following normal pregnancy. The delivery was normal. No record of labour stimulation is available, but 0.7 ml pituitrine was given. The cord was wound around the infant's neck, but she was not asphyxiated. Because of cyanotic attacks she was admitted to the DPGs during the first 24 hours with diagnosis of asphyxia. On admission she was flaccid and her respiration was grunting. She sustained repeated cyanotic attacks during the first 24 hours only. Her respiration and muscle tone quickly became normal. She was discharged 3 days later in apparently good condition.

Diagnosis: congenital debility

second day he was admitted to the DPGs because of suspected intracranial haemorrhage and hyperpyrexia (39 °C). On admission he was restless and trembling, but not rigid, his colour was good. He recovered quickly and his temperature fell to normal within 24 hours. He was discharged after 6 days in apparently good condition.

The diagnosis: suspected intracranial haemorrhage.

His growth was normal, as was his motor development, though for the first few months he was rather flaccid and listless; he did not smile until 5 months or so up until about 9 months, but walked at 15 months. The motor pattern was normal. His mental development was apparently quite satisfactory. Nevertheless the family doctor, suspecting retarded development, had him referred, at 2½ years, for psychological examination. His DQ was found to be 94 at Bühler Heizer infant-testing. The child was considered of normal intelligence, and the low score recorded was thought to be due to his speech defect. His speech, which was bizarre and almost unintelligible, was interpreted as an isolated expressive aphasia. There were no receptive speech disorders. He was restless and could not concentrate, which was ascribed to illness. He was referred to the Institute for Speech Disorders. However shortly after entering kindergarten his speech improved spontaneously and the examination was not carried out.

On follow-up examination, at 5 years 9 months, he was found to be well-developed, physically and mentally. The neurological examination was normal. His speech was characterized by mispronunciation of certain consonants (the mother thought it was normal), vocabulary and speech comprehension appeared normal. EEG was not carried out. At about 6 years of age he was again referred to the Institute for Speech Disorders, where he was found to have a slight speech defect. However his greatest problem was, in their opinion, his restlessness and lack of concentration, even though these features had improved. Since schooling problems, particularly in reading, were anticipated, he was referred to a school psychologist with a view to postponing school attendance for a year. It is not known, however whether this examination was carried out or not.

Diagnoses: previous mild motor retardation, dysphasia, behaviour difficulties.

No 44 (19894/3/1953)

A boy born at term in a private clinic on Febr 16, 1953 to a multipara, following a normal pregnancy. The delivery was prolonged, stimulated by injections repeatedly 1 ml of pethidine was also given. The course was normal. The infant was not asphyxiated however he was admitted to the DPGs at 8 days because of poor sucking and grunting respiration and suspected atelectasis. On admission his breathing was rather laboured, but quickly improved, and no other symptoms were observed. He was discharged in apparently good condition 3 days later.

Diagnosis: congenital debility.

His later growth, motor and mental development were normal. He began to say single words at 18 months, but was rather late in forming sentences, and there were a few defects of pronunciation.

At follow-up 5½ years old, he could not talk correctly but his vocabulary was felt to be within normal limits. Hearing was normal. His motor and mental development were also considered normal. Neurological examination was normal.

EEG was recommended, but his parents were not interested.

Diagnoses: speech retardation, mild dysphasia.

No 45 (22105/3/1953)

A boy born in a private clinic at term on March 28 1953 to a 30-year-old primipara, following an uncomplicated pregnancy. The delivery which was prolonged, was stimulated by injections, pethidine was given and forceps were applied. There was prolonged asphyxia. Methods of resuscitation were not mentioned. The infant was transferred immediately to the DPGs suspected of intracranial haemorrhage. On ad-

She was 4½ years old at follow-up. Her physical and mental development was considered normal for her age. She still had faulty pronunciation of a few consonants, but her vocabulary was considered adequate for her age. There was pronounced convergent strabismus. The neurological examination was normal.

Diagnosis: previous poor growth, convergent squint (familial), speech retardation, mild dysphasia.

No. 50 (13918/3/1954)

A girl born at home at term on Oct. 3 1954, to a primipara following normal pregnancy. The delivery was prolonged, but otherwise apparently normal. It was stimulated by injections and pituitrin was also given. The infant was asphyxiated for about 20 minutes. There is no record of resuscitation. Her condition appeared normal during the first 24 hours of life, but on the second day she developed cyanotic attacks, during which she was drowsy. She was admitted to the DPGs with a diagnosis of asphyxia. On admission she was flaccid and drowsy and she exhibited during the first day four cyanotic attacks. Subsequently she improved rapidly and her condition was normal at discharge, after 6 days.

Diagnosis: congenital debility sequelae of asphyxia.

Growth and development were satisfactory. She sat up at 4 months and walked at 12 months. Her motor pattern was normal. Hearing and vision were also normal. She started to talk at about 18 months, though not properly. At 2½ years she entered kindergarten, after which her speech improved somewhat. Her mental development was satisfactory: she presented no behaviour problems, though she was extremely restless during her first year of life. There was no explanation for this.

When seen at follow-up at 4 years she had developed physically and mentally to her own age. She pronounced a few consonants incorrectly but her vocabulary was considered adequate for her age. The neurological examination was normal.

Diagnosis: previous hyperactivity slight retardation of speech, mild dysphasia.

No. 51 (13923/3/1954)

A boy born at home at term on April 25, 1954 to a multipara following a normal pregnancy. He was born as first twin by breech presentation. There is no information concerning the use of labour stimulation or morphine. He was not asphyxiated and apparently presented no abnormal features for the first two days. On the third day however he suffered repeated cyanotic attacks and was referred to the DPGs for observation. On admission he was flaccid and sucked poorly. On that day he exhibited further cyanotic attacks, but these were not repeated. His condition improved gradually and he was discharged 9 days later in apparently good condition.

Diagnosis: congenital debility

His growth and development were normal. He walked at the usual time. His vision and hearing were normal. He talked at about 2 years, with some errors of pronunciation. There were no behavioural problems; but he had nocturnal convulsions (which was familial).

At follow-up, at 5 years of age, he had scarcely reached medium height (unlike 6 cm), but was well-proportioned and well-nourished. His mental development appeared comparable with his age. He pronounced a few consonants incorrectly but his vocabulary appeared normal. The neurological examination was normal.

Diagnosis: nocturnal (familial) convulsions, mild dysphasia.

No. 52 (768/3/1948)

A boy born at home, possibly 3 weeks beyond term, on Nov. 20, 1948, to a multipara of 35 years, following normal pregnancy. The delivery seems to have been normal, use of labour stimulation and morphine is not reported. He was delivered by vigorous manual expulsion. BW 4200 g. There was apparently no asphyxia or other abnormal features during the first 24 hours. On the second day however he

Her growth and development were normal. She walked at one year. Her mental development was satisfactory and she presented no behavioural problems. Her vision and hearing were normal. She was able to say single words before the age of one. However she could not form sentences until she was 3 years of age and her pronunciation was faulty.

At follow-up, 4 1/2 years old she still spoke incorrectly however her vocabulary was felt to be normal. Her mental development appeared compatible with her age. Her physical development was normal. The neurological examination was normal. EEG was not recorded.

Diagnosis: speech retardation, mild dysphasia.

No 48 (16757/205/1955)

A boy born in a private clinic at term on Oct. 30, 1955 to a multipara of 40 years, following a normal pregnancy. The delivery was prolonged, but otherwise uncomplicated. Stimulating injections were given twice. Pethidine was also given twice and tetrapon once. There was "prolonged" asphyxia and the infant was given lobeline and artificial respiration. Immediately afterwards he was transferred to the DPGc with a diagnosis of congenital debility. On admission he was restless, trembling and rigid. The rigidity was more pronounced in the right side. Respiration was grunting. During the first three days the patient exhibited repeated cyanotic attacks, as well as convulsions, which were more pronounced in the right side. There was a high-pitched cry. Oxygen was administered for 3 days, after which the condition became normal, and he was discharged on the 6th day in apparently good condition. Follow-up was recommended however.

Diagnosis: difficult birth, suspected intracranial haemorrhage.

He was seen in the OP-clinic of the DPGc at 6 months and was found to be normal as far as his mental and motor development was concerned. He could sit up alone, was alert and interested. His muscle tone was normal. Growth and development were satisfactory also thereafter. He walked at 11 months and his motor pattern was normal. His vision and hearing were normal. He began to say single words at one year but at 3 years he could still not form sentences. His pronunciation was correct.

At follow-up, when three years old, his mental and motor development was considered compatible with his age. The neurological examination was normal. His speech was faulty as mentioned. EEG was not recorded.

Diagnosis: speech retardation (?).

No 49 (8623/3/1954)

A girl born in a private clinic at term on July 26, 1954, to a 31 year-old multipara following a normal pregnancy. The delivery was normal, labour stimulation and morphia were not given. There was asphyxia for a few minutes, and cyanotic attacks occurred during the first 24 hours. The infant was therefore transferred to the DPGc. The cyanotic attacks persisted for three days. Repeated convulsions, more pronounced in the right side, were observed during the same period. There was also a bilaterally equal rigidity. From the fourth day onwards there were no further attacks. However on discharge, on the eighth day there was some rigidity of the back. Her general condition otherwise was good.

Diagnosis: asphyxia neonatorum, suspected intracranial haemorrhage.

Her growth was slow for the first two years, but thereafter improved. During the same period she frequently ground her teeth. There was a convergent squint, but her vision was thought to be good and no treatment was given. (A sister had a squint). The motor development was good. She sat up at 6 months, and walked at one year. The motor pattern was normal. Her hearing was good. She said single words at 2 years and talked by the time she was 3 with faulty pronunciation of a few consonants. Her mental development was satisfactory. No behaviour problems were reported.

to certain problems due to restlessness and hyperactivity. Her vision, hearing and speech were normal. About 4 years of age she suffered a generalized clonic seizure in connection with a febrile illness. There was no other history of convulsions or family history.

At follow-up, 5 years of age, she was found to be normally developed physically as well as mentally. The neurological examination was normal. She had nocturnal convuls (non-familial). For geographical reasons an EEG was unobtainable.

Diagnosis: febrile convulsions (late onset), behaviour disorder, nocturnal convulsions.

Na. 55 (Q1621/3/1955)

A girl born at home at term on Jan. 14, 1955, to a multipara following a normal pregnancy. Delivery was normal. Labour was not stimulated or morphine given. The infant was not asphyxiated. However during the first 24 hours she developed cyanosis and apnoea lasting for a few minutes. When these symptoms recurred on the second day, she was admitted to the DPGs. On that day two further attacks occurred, but otherwise no abnormal features were observed, and she was symptomless for the rest of her 6 days' stay. On discharge her condition seemed good.

Diagnosis: congenital debility.

Her growth and development, physical as well as mental, were satisfactory. She walked at 13 months, and her motor pattern was normal. Hearing and speech were normal. Apart from a divergent squint (familial) her vision was normal. At the age of two years she had a generalized clonic convulsion lasting for a few minutes in association with high fever, and on two further occasions there was gross trembling in association with fever. There was no familial history of convulsions.

At follow-up, at the age of 4, her physical and mental development were found to be compatible with her age. The neurological examination was normal. She had a slight divergent squint. EEG was normal.

Diagnosis: febrile convulsions, familial divergent squint.

Na. 56 (R165/3/1954)

A girl born at home before term on July 18, 1954, to a multipara following a normal pregnancy. She was the second twin. The delivery was apparently normal. Labour stimulating injections were given. There is no record of the use of morphine. BW was 1800 g. The infant was not asphyxiated. (The first born twin died at home on the second day from unknown cause). She was admitted to the DPGs on the second day with diagnosis of prematurity appeared normal on admission, but suffered repeated cyanotic attacks on the third day of life. Thereafter she was well and 18 days later was discharged in apparently good condition.

Diagnosis: congenital debility, prematurity.

Her growth was satisfactory and her motor development good, she walked at 15 months. Her motor pattern was normal. She had convergent squint (non-familial). Her hearing was normal. She talked "early". Up to the age of 18 months she had several (as described as breath holding spells). (No family history of convulsion reported). Her mental development was satisfactory and she presented no behavioural problems.

She was seen at follow-up aged 4½ years, at which time her height was 8 cm below average (non-familial); she was well-proportioned, though slight, but well-nourished. Her motor pattern was normal. Mental development appeared normal for her age. The neurological examination was normal. There was mild convergent squint.

Diagnosis: convergent squint, breath holding spells (in the past), small size.

N. 57 (J252/3/1951)

A boy born on June 15, 1951, to a 34-year-old multipara. The pregnancy had been complicated by severe varicose veins and oedema of the legs, and the delivery was therefore induced at term in private clinic. Repeated labour stimulative injections

suffered convulsions and cyanotic attacks and was admitted to the DPGs suspected of birth injury. On admission he was flaccid, and his respiration was grunting. He sucked poorly. During that day and the following he sustained additional cyanotic attacks and two generalized seizures. His condition improved gradually, his respiration and tone became normal, and on discharge, after 19 days stay his condition was considered good.

Diagnosis: intracranial haemorrhage.

His growth was slow throughout his childhood though his motor development was normal. He sat up at 6 months and walked by 10 months. The motor pattern was normal, as were his vision and hearing. He spoke at 2 years. Nocturnal enuresis was present until 9 years (not familial). He started school at 7 years. His progress, however, was poor and after 3 months, school attendance was postponed for another year. The school psychologist at that time found his IQ to be 80. The next year he did not do much better. At the end of the year he was tested again, revealing an IQ of 84. He was particularly poor at arithmetic. The school psychologist found no evidence of brain damage. The boy was transferred to a special class, where he did better. He presented no behavioural problems.

When seen at follow-up, 11½ years old, he was small—20 cm below average height (no family history of small size) and rather slight, but well-proportioned. He appeared backward, but well-balanced. The neurological examination was normal. EEG was normal.

Diagnoses: small size, mental retardation (backwardness), previous nocturnal enuresis.

No. 53 (8347/3/1954)

A boy born at home at term on July 22, 1954 to a 33-year-old multipara following a normal pregnancy. The delivery was rapid. No drugs were given. The infant was asphyxiated for a few minutes. No treatment was given. Because of cyanotic attacks he was admitted to the DPGs during the first 24 hours with a diagnosis of congenital debility. During his first day in hospital he exhibited additional attacks of cyanosis as well as intermittent apnoea. Subsequently there were no abnormal features and he was discharged 5 days later in apparently good condition.

Diagnosis: asphyxia neonatorum.

His growth was normal, his mental and motor development were satisfactory. He walked at 10 months. His vision and hearing were normal. He talked at 2 years of age and presented no behavioural problems. He occasionally ground his teeth at night.

When seen at follow-up, not quite 4½ years old, he was about 10 cm under average height, though well-proportioned and well-nourished. His motor pattern was normal and mental development appeared in line with his age. He still had enuresis at night. (No family history of small size or enuresis).

Diagnoses: small size, nocturnal enuresis.

No. 54 (24866/3/1954)

A girl born in a private clinic before term on March 20, 1954 to a primipara following a normal pregnancy. The delivery was normal; stimulating injections or morphia were not given. There was asphyxia for a few (7) minutes, during which lobeline and coramine were given. BW was 2100 g. She was admitted to the DPGs shortly after birth with a diagnosis of congenital debility due to slight respiratory trouble. Her breathing was grunting on admission, but otherwise she was quite well. During her second and third day she sustained additional cyanotic attacks, and her respiration was still laboured but thereafter improved. During the rest of her 17 days stay she presented no abnormal features and her condition appeared good on discharge.

Diagnosis: congenital debility.

Her growth and development were good. She walked at one year. Her motor pattern was normal and her mental development was satisfactory. Her behaviour gave rise

to certain problems due to restlessness and hyperactivity. Her vision, hearing and speech were normal. About 4 years of age she suffered a generalized clonic seizure in connection with a febrile illness. There was no other history of convulsions or family history.

At follow-up, 5 years and 3 months of age, she was found to be normally developed, physically as well as mentally. The neurological examination was normal. She had nocturnal convulsions (non-familial). For geographical reasons an EEG was unobtainable.

Diagnosis: febrile convulsions (late onset), behaviour disorder nocturnal apnoeas.

No. 55 (21621/3/1955)

A girl born at home at term on Jan. 14, 1955 to multipara following a normal pregnancy. Delivery was normal. Labour was not stimulated or morphine given. The infant was not asphyxiated. However during the first 24 hours she developed cyanosis and apnoea lasting for a few minutes. When these symptoms recurred on the second day she was admitted to the DPGs. On that day two further attacks occurred, but otherwise no abnormal features were observed, and she was symptomless for the rest of her 6 days' stay. On discharge her condition seemed good.

Diagnosis: congenital debility.

Her growth and development, physical as well as mental, were satisfactory. She walked at 13 months, and her motor pattern was normal. Hearing and speech were normal. Apart from a divergent squint (familial) her vision was normal. At the age of 1½ years she had a generalized clonic convulsion lasting for a few minutes in association with high fever, and on two further occasions there was gross trembling in association with fever. There was no familial history of convulsions.

At follow-up, at the age of 4, her physical and mental development were found to be compatible with her age. The neurological examination was normal. She had slight divergent squint. EEG was normal.

Diagnosis: febrile convulsions, familial divergent squint.

No. 56 (8165/3/1954)

A girl born at home before term on July 18, 1954, to multipara following a normal pregnancy. She was the second twin. The delivery was apparently normal. Labour stimulating injections were given. There is no record of the use of morphine. BW was 1800 g. The infant was not asphyxiated. (The first born twin died at home on the second day from unknown cause). She was admitted to the DPGs on the second day with a diagnosis of prematurity appeared normal on admission, but suffered repeated cyanotic attacks on the third day of life. Thereafter she was well and 38 days later was discharged in apparently good condition.

Diagnosis: congenital debility prematurity.

Her growth was satisfactory and her motor development good, she walked at 15 months. Her motor pattern was normal. She had convergent squint (non-familial). Her hearing was normal. She talked early. Up to the age of 18 months she had several fits described as breath holding spells. (No family history of convulsion reported). Her mental development was satisfactory and she presented no behavioural problems.

She was seen at follow-up aged 4½ years, at which time her height was 3 cm below average (non-familial), she was well-proportioned, though slight, but well-nourished. Her motor pattern was normal. Mental development appeared normal for her age. The neurological examination was normal. There was mild convergent squint.

Diagnosis: convergent squint, breath holding spells (in the past), small size.

No. 57 (5252/3/1951)

A boy born on June 15 1951 to 34-year-old multipara. The pregnancy had been complicated by severe varicose veins and oedema of the legs, and the delivery was therefore induced at term in a private clinic. Repeated labour stimulating injections

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGs on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis: congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved but his height remained sub-normal. (Both parents were small). He sat up at 8-9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months—two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizure-free.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow-up, at 7 1/2 years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnosis: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No. 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nitethamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGs at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blagdanahospital) however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnosis: previous motor retardation, previous benign hypotonicity

No. 59 (570/1/1946)

A boy born at the RH before term on Oct. 18, 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was asphyxiated for

15 minutes, during which lobeline was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGs on the 12th day. Here his growth was poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slower no information was available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time, but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13-14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnosis: previous motor retardation, previous poor growth, dyslexia.

A. 60 (57/3/1946)

A boy born on March 20, 1946, to multipara following normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphine is not reported. The infant had the cord wound around his neck, but apparently was not asphyxiated. He was admitted to the DPGs in the first 24 hours because of cyanosis and fever with diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-ray gave no confirmation and maculation also was normal. He sucked poorly and had to be given oxygen for the first 5 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good, during his first two years his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGs because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of two years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslexic and received special education for some time.

He was followed-up at more than 12 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly probably because of rather pronounced flatfoot. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EKG had not been carried out.

Diagnosis: previous motor retardation, previous benign hypotonicity bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGs on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis: congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved but his height remained sub-normal. (Both parents were small). He sat up at 8-9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months—two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizure-free.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow-up, at 7 1/2 years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnoses: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No. 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGs at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet); however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnosis: previous motor retardation, previous benign hypotonicity

No. 59 (570/1/1946)

A boy born at the RH before term on Oct. 18 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was asphyxiated for

15 months, during which lobeline was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGs on the 12th day. His growth as poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slow: no information was available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time, but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13-14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnosis: previous motor retardation, previous poor growth, dyslexia.

No. 60 (578/3/1946)

A boy born on March 20, 1946, to multipara following normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphine is not reported. The infant had the cord wound around his neck, but apparently was not asphyxiated. He was admitted to the DPGs in the first 24 hours because of cyanosis and fever with a diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-rays gave no confirmation and auscultation also was normal. He sucked poorly and had to be given oxygen for the first 5 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good; during his first two years his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGs because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of 2-0 years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslexic and received special education for some time.

He was followed-up at more than 12 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly probably because of rather pronounced flatfeet. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EEG had not been carried out.

Diagnosis: previous motor retardation, previous benign hypotonicity, bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated, but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGs on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis: congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved, but his height remained sub-normal. (Both parents were small). He sat up at 8-9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months—two years. At about one year he sustained an attack of generalized tonic convulsions in association with high fever but was thereafter seizure-free.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow-up, at 7 1/2 years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnosis: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGs at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet), however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnosis: previous motor retardation, previous benign hypotonicity

No 59 (570/1/1946)

A boy born at the RH before term on Oct. 18, 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was asphyxiated for

15 minutes, during which lobalase was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGs on the 12th day. Here his growth was poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slow: no information is available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13-14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 1/2 years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnosis: previous motor retardation, previous poor growth, dyslexia.

No. 60 (578/3/1946)

A boy born on March 20, 1946, to a multipara following a normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphine is not reported. The infant had the cord wound round his neck, but apparently was not asphyxiated. He was admitted to the DPGs in the first 24 hours because of cyanosis and fever with a diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-ray gave no confirmation and auscultation also was normal. He sucked poorly and had to be given oxygen for the first 3 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good during his first two years; his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGs because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of two years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslexic and received special education for some time.

He was followed-up at more than 11 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly. Probably because of rather pronounced flatfoot. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EEG had not been carried out.

Diagnosis: previous motor retardation, previous benign hypotonicity, bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated, but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGs on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis: congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved, but his height remained sub-normal. (Both parents were small). He sat up at 8-9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months—two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizure-free.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow up, at 7½ years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnosis: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No 38 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, in a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikelthamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGs at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet); however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnosis: previous motor retardation, previous benign hypotonicity

No 59 (5/0/1/1946)

A boy born at the RH before term on Oct. 18 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was asphyxiated for

to talk at 18 months, and his pronunciation was correct. His mental development was satisfactory and there were no behaviour problems.

At the age of 3, at follow-up, he was found to be physically and mentally developed according to his age. The neurological examination was normal.

Diagnosis: previous motor retardation, previous benign hypotonicity

No. 64 (18791/3/1955)

A girl born at term at home on Oct. 31 1953 to a multipara, who suffered rubella during the third month of gestation. The delivery was uncomplicated, labour stimulation and morphia were not applied. BW was 2900 g. The infant was not asphyxiated, but listless, flaccid and sucked poorly. However she was not admitted to the DPGs until 3 days later. The diagnosis was prematurely suspected intracranial haemorrhage. On admission the above mentioned features were observed. Subsequently there were varying opinions on her muscle tone; one examiner found it to be upper borderline normal. At discharge it was normal. 2-3 weeks after admission her growth became satisfactory and she was discharged after 29 days in apparently good condition.

Diagnosis: congenital debility suspected intracranial haemorrhage.

Since her growth and development were slow she was readmitted at the age of 4 months. The examination revealed marked rickets, and because of decreased tendon reflexes and certain tension of the adductor muscles in the legs spasticity was suspected. The child was in poor condition and emaciated. A gluten-free diet was tried with no results.

Her growth remained unsatisfactory until the age of 2 years; after which it improved. During this period she was also listless, flaccid and her need for sleep was great. Her motor development was slow she did not sit up until she was 9-10 months and walked at about 20 months. Her motor pattern appeared normal. Her vision, hearing and speech were normal.

She was seen at follow-up before she was 3½ years old. Her height and weight are average. Head circumference was lower borderline normal (48 cm). Her intellectual development seemed in line with her age. The neurological examination was normal.

Diagnosis: previous motor retardation, previous hypotonicity previous poor growth, previous rickets.

No. 65 (934/3/1948)

A boy born at home before term on Jan. 9 1948, to multipara following normal pregnancy. During the delivery quinine was administered. In addition labour stimulant injections were given three times, but no morphia was given. Otherwise the course seemed to have been normal. BW was 1800 g. The infant was not asphyxiated. He sucked poorly and did not gain weight at home but was otherwise apparently normal. He was admitted to the DPGs at 19 days with diagnosis of congenital debility. Apart from persistently poor sucking and slow growth he exhibited no abnormal features during the 64 days in hospital. He was discharged in apparently good condition.

Diagnosis: prematurely congenital debility

His growth was unsatisfactory for further 2 months. However from the age of four months it improved. His motor development was slow he did not sit up until he was one year old and did not walk until over 18 months old. His motor pattern was felt to be normal. His vision, hearing and speech are also normal; he talked at 2-3 years. His mental development was fairly good. He started school at the usual time, but had to repeat the first form. Thereafter his progress was satisfactory but he had reading difficulties and was thought to be mildly dyslectic. There were no major behaviour problems; he got on quite well with other children, but had somewhat violent temperament. He had been psychologically tested twice, but the outcome is not known.

When he was seen at follow-up, at the age of 10, his physical development was

No 61 (14446/3/1952)

A girl born in a private clinic before term on Dec. 1 1952, to a multipara following normal pregnancy. The delivery was normal. Pethidine was given, there was no record of labour stimulation. BW 2000 g. The infant was not asphyxiated, but was immediately admitted to the DPGs because of low BW. On admission the respiration was grunting and during the first 4 hours there were a few cyanotic attacks. Oxygen was given for 4 days, and thereafter the respiration became normal. The infant revealed no further abnormalities and was discharged after 22 days in apparently good condition.

Diagnosis: prematurity suspected intracranial haemorrhage.

The subsequent growth was satisfactory. The motor development was fairly satisfactory. She sat up at 6 months, but did not walk until 2 years of age. The motor pattern was normal. Vision, hearing, speech, mental development and behaviour were normal. She had, however, been very restless for no apparent reason during the first two years of life. She was expected to be ready for school at the usual time.

On follow-up, at the age of 6, her physical and mental development was found to be normal. The neurological examination was normal.

Diagnosis: previous motor retardation, previous hyperactivity

No. 62 (7215/3/1954)

A boy born in a private clinic at term on July 6 1954 to a primipara following a normal pregnancy. The membranes had ruptured 2 days prior to delivery but labour did not occur. Hence the delivery was stimulated by several injections. There was no record of morphia being used. The course was uncomplicated. BW was 2750 g. He was not asphyxiated but suffered a cyanotic attack on the first day and was referred to the DPGs. On admission he was trembling and his respiration grunting. However he recovered within a day or so and the cyanotic attacks did not recur. He was discharged on the 8th day in apparently good condition.

Diagnosis: sequelae of difficult delivery

His growth was poor for the first few months, during which he was also very listless. Subsequently he gradually became more active, and his growth improved. He sat up at 8-9 months and walked at 14 months. His motor pattern was normal. At the age of 6 months impaired hearing was suspected but this was not confirmed. He talked when well over 2 years old. His vision was normal. His mental development and behaviour were satisfactory.

On follow-up examination, at the age of 4 1/2 years, his physical and mental development was found to correspond to his age. The neurological examination was normal.

Diagnosis: previous mild motor retardation, previous poor growth.

No. 63 (16182/35)

A boy born at home at term on Oct. 23 1955 to a multipara, following a normal pregnancy. The delivery was uncomplicated. Labour stimulation but no morphia was given. There is no mention of asphyxia, however lobeline was given. The infant was referred to the DPGs immediately after birth diagnosed as "Rhesus baby" the mother being Rh-negative. The infant, however was also Rh-negative, and did not develop jaundice. On admission he was flaccid with grunting respiration and during the first 24 hours exhibited two cyanotic attacks. He recovered rapidly and oxygen therapy was discontinued after 2 days. The flaccidity disappeared within forty-eight hours, and thereafter he appeared normal until his discharge on the 5th day.

Diagnosis: congenital debility

During the first 10 months of his life the parents suspected brain damage, since he appeared very listless and passive. He did not smile and focus until he was 6 months old. He did not sit up until 10 months. From then on he started to develop rapidly and in a normal way. He walked at 14 months, and his motor pattern was normal. His vision and hearing were felt to be within normal limits. He began

stimulation or morphia being used. The infant was not asphyxiated. However she was admitted to the DPGs within the first 24 hours because of cyanotic attacks and an episode of generalized convulsions, with a diagnosis of intracranial haemorrhage, cephal-haematoma. The latter was confirmed, but no other abnormalities were found during her 7 days stay and she was discharged in apparently good condition.

Diagnosis: suspected congenital debility

Her growth and development were normal. She walked when over one year of age, and her motor pattern, mental development, vision, hearing and speech were all normal. She talked at 18 months. During the first two years of life she was markedly restless, for which no external cause could be found. Her need for sleep was very reduced. After that time her behaviour was unremarkable; she played well and was quiet.

When seen at follow-up at 5 years of age she was well above average height and well-nourished. Her physical development was compatible with her age. Her intelligence was felt to be normal. The neurological examination was normal.

Diagnosis: previous hyperactivity

No. 69 (14942/3/1954)

A boy born in a private clinic at term on Oct. 15 1954, to a primipara of 24 years, following a normal pregnancy. The delivery was induced, but the indication for this is not clear. Repeated stimulant injections were given, as well as morphia. The course was prolonged. As no progress was made, despite adequate labour forceps were applied. The infant was apparently not asphyxiated, nor did he present any abnormal features during the early days of life. However he was admitted to the DPGs on the fifth day because of suspected intracranial haemorrhage. On admission he was cold and flaccid, however his colour was good. He sucked poorly but recovered quickly without presenting additional symptoms. After 6 days he was discharged in apparently good condition.

Diagnosis: sequelae of difficult birth, suspected intracranial haemorrhage.

His growth, physical and mental development, vision, hearing and speech were all normal. The only abnormal feature observed was marked restlessness during the first 9 months or so. No external cause for this could be established.

He was seen at follow-up at the age of 4 years. His physical and mental development was compatible with his age and the neurological examination was normal.

Diagnosis: previous hyperactivity

No. 70 (1467/3/1955)

A boy born in a private clinic at term on April 25 1955 to a primipara following normal pregnancy. The delivery was uncomplicated, though powerful stimulation by drugs was applied and morphia was given. The infant exhibited prolonged asphyxia, during which lobeline, oxygen and artificial respiration were given. Immediately after birth, when transferred to the DPGs, he was flaccid, cyanosed and apnoeic. He was given oxygen, and following two hours of artificial respiration and 0.2 ml of lobeline his respiration became spontaneous and gradually regular. He was given oxygen for two days, after which his colour remained satisfactory when oxygen was discontinued. He presented no further symptoms thereafter and was discharged after 6 days, in apparently good condition.

Diagnosis: asphyxia neonatorum.

He was seen in OP of the DPGs at 3 months. His growth had been satisfactory and his development good. No neurological signs were demonstrated.

His growth remained satisfactory and his motor development was also adequate. He sat up at 6 months and walked at 12. His motor pattern, vision, hearing and speech were normal. He talked at 2 years. His mental development and behaviour were good, though he was extremely restless during the first 18 months, and particularly during sleep. This feature could not be explained by environmental factors.

Diagnosis: previous hyperactivity

compatible with his age. Mentally he appeared essentially normal, though perhaps somewhat backward. The neurological examination was normal. EEG was recommended, but refused by his parents.

Diagnosis: previous motor retardation, minor behaviour difficulties, previous poor growth, mild mental retardation? dyslexia?

No 66 (6375/3/1952)

A boy born in a private clinic almost at term on July 15, 1951, to a primipara, who during pregnancy repeatedly had experienced slight vaginal bleeding. The delivery was prolonged and several stimulant injections were given, besides pethidin on two occasions. The course was otherwise uncomplicated. BW was 2400 g. The infant was asphyxiated for a few minutes during which he was given coramine and lobeline. On the fifth day he was transferred to the DPGs because of suspected intracranial haemorrhage. He had been restless and had sucked poorly and continued to present these features during admission. His respiration was somewhat grunting to begin with, but was quickly restored to normal. He recovered within a few days and his growth gradually became satisfactory. He was discharged after 21 days in apparently good condition.

Diagnosis: congenital debility

His growth was unsatisfactory for two years and then improved. He was followed-up as OP at the RH at 9 months of age because of anorexia. X-rays revealed no organic explanation for this feature. His motor development at first was slow: he sat up at 11 months, walked at 15 months. His motor pattern, vision, hearing and speech were all normal. He talked properly at 18 months. His mental development was satisfactory. He was rather restless, which might, to a large extent, be explained by sibling-jealousy.

When seen at follow-up, not yet 6½ years old, his height was just below average (minus 5 cm), but he was well-proportioned and well-nourished. His motor pattern was normal. His mental development was felt to be adequate. The neurological examination was normal so was EEG.

Diagnosis: previous moderate motor retardation, previous poor growth.

No 67 (8703/3/1951)

A boy born at term in a private clinic on Aug. 29 1951 to a 35-year-old multipara, following an uncomplicated pregnancy. The delivery was induced by rupture of the membranes and injections, though the indication for this is obscure. Morphosis was not given. The course was uncomplicated. The infant was not asphyxiated. He was transferred to the DPGs within the first 24 hours because of flaccidity and cyanotic attacks, the diagnosis being suspected tentorial tear. On admission there was flaccidity and grunting respiration, and during the first 3 days there were several cyanotic attacks. Following oxygen therapy he improved, his tone and respiration became normal and he was discharged after 8 days in apparently good condition.

Diagnosis: congenital debility

His growth and development were satisfactory. He sat up at 6 months, walked at 14 months, and his motor pattern, mental development and behaviour were normal. He was expected to be ready for school at the usual time. His vision, hearing and speech were normal. During his first two years of life he was very restless and screaming, and his sleep was disturbed. These features gradually subsided. Precipitating factors in his environment were not disclosed.

When followed-up at 6 years 8 months of age his physical and mental development was found to be compatible with his age. The neurological examination was normal.

Diagnosis: previous hyperactivity

No 68 (61/3/1953)

A girl born at home at term on April 1 1953 to a 35-year-old multipara, following an uncomplicated pregnancy. The delivery was normal. There is no record of labour

let to asphyxia. The course was uncomplicated. The infant was asphyxiated for about 15 minutes and was given lobeline. Two hours after birth he was admitted to the DPGs with a diagnosis of congenital debility. On admission he exhibited flaccidity and grunting respiration; his colour was good except for harlequin colour change on two occasions. He made a rapid recovery and was discharged after 4 days in apparently good condition.

Diagnosis: congenital debility

His growth and motor development were normal. He walked by the time he was one and his motor pattern was normal. His vision and hearing were good. He had mild squint (familial). He talked at about 2-3 years; his mental development was felt to be normal, though he had a "nervous disposition" and was easily frightened. He also exhibited violent temper tantrums and there was nocturnal teeth grinding with decreasing frequency.

He is mentally and physically developed in line with his age, when seen at follow up at 4½. His behaviour appeared normal during the examination. Neurological examination and EPG were normal.

Diagnosis: behaviour disorder, convergent squint (familial).

No. 74 (9403/1954)

A boy born in private clinic at term on Aug. 11 1954 to a multipara of 40 years (her last delivery had occurred 17 years earlier). The pregnancy was uneventful. Because the delivery did not progress, repeated stimulant injections were given. There is no record of the use of morphine. The course was otherwise normal. The cord was wound around the infant's neck. He was asphyxiated for a few minutes and was given lobeline. Within the first 4 hours he was admitted to the DPGs because of generalized convulsions. On admission his colour was good, but he was markedly rigid and during the second day of life again developed generalized clonic seizure. His tone quickly returned to normal and his condition thereafter was normal. He was discharged after 5 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

Re-examination at 3 months was recommended. However he failed to attend at this time.

His growth and motor development were satisfactory: he walked at one year. His vision, hearing and speech were normal. He talked adequately at 2-3 years. His mental development was satisfactory though he was markedly restless. His mother attributed to his being quite spoiled.

When seen on follow-up examination at four years his physical development was compatible with his age, though he seemed rather babyish, his intelligence was felt to be adequate. An EEG carried out one year later was normal. At that time he was still very fidgety and irritable. A psychological examination was suggested, but could not be carried out.

Diagnosis: behaviour difficulties.

No. 75 (403/3/1947)

A boy born in private clinic at term on Aug. 31 1947 to a primipara following a normal pregnancy. The delivery was prolonged, but apparently uncomplicated. No information is available concerning labour stimulation or morphine. BW was 4200 g. The cord was wound around the infant's neck, and he was asphyxiated for about 20 minutes, during which time he was given oxygen, artificial respiration, lobeline and cardanol. He developed generalized clonic convulsion and was immediately transferred to the DPGs with a diagnosis of tentorial tear. On admission he was rigid, and during the first 3 days of life he had several convulsions. His muscle tone gradually returned to normal and no other abnormal features were observed. He was discharged after 18 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth and motor development were good, he sat up at 6 months and walked

No 71 (20844/3/1955)

A girl born at the RH at term on Dec. 7 1955 to a multipara following a normal pregnancy. The delivery was prolonged, but uncomplicated. One labour stimulating injection but no morphia was given. The infant was not asphyxiated. However because of cyanotic attacks during the first 24 hours she was transferred to the DPGs suspected of a heart defect. Chest X rays revealed atelectasis, but no evidence of heart disease, and auscultation was also normal. On admission she was flaccid, and presented grunting respiration as well as cyanotic attacks, which persisted until the 4th day or so. After that date her colour and respiration were normal she was still rather flaccid and sucked poorly. Her muscle tone was gradually restored to normal, but her growth remained poor. At 3 weeks she developed a severe gastro-enteritis caused by *Coli* 111. She was treated with parenteral fluids and antibiotics and improved fairly rapidly. From about one month of age her growth improved. She was discharged after 50 days apparently in good condition but follow-up was recommended.

Diagnosis: asphyxia, gastro-enteritis (*Coli* 111).

Her growth was satisfactory and her motor development good. She sat up at 6 months, but did not walk until 18 months. Her motor pattern, vision, hearing and speech were all normal. She talked at about 2 1/2 years. Her mental development was satisfactory. However during her first two years of life she showed conspicuous restlessness and fits of screaming for no obvious reasons. Thereafter she was still rather lively but cheerful, and there was no further unmotivated restlessness.

When followed-up at over 3 years of age her height was just below average however she was well-proportioned and well-nourished, and her motor pattern was normal. Mental development appeared compatible with her age. The neurological examination was normal.

Diagnosis: previous hyperactivity

No 72 (15934/3/1952)

A boy born in a private clinic at term on Dec. 29 1952, to a 34-year-old multipara following a normal pregnancy. The delivery was normal stimulant injections were given twice and full anaesthesia was applied. BW was 4000 g. There is no record of asphyxia, but lobeline was given. He was admitted to the DPGs on the first day because of cyanotic attacks and suspected pulmonary atelectasis. During that day he sustained two further cyanotic attacks, but these were not repeated, and he was otherwise normal and able to be discharged 2 days later in apparently good condition.

Diagnosis: aspiration into the lungs.

His growth and motor development were normal. He sat up "early" and walked at 15 months. His motor pattern was normal. He had a squint. Diminished visual acuity in the right eye was disclosed and glasses were provided. His parental grandfather also had a squint. His hearing was normal. He spoke by the time he was 2-3 years with a transitory stammer. His mental development was satisfactory though he was irritable and sensitive. He was also over-sensitive to noise.

On follow-up, at the age of 5 1/2, his physical development was compatible with his age. Mentally he appeared normal though somewhat reserved. His speech was normal. He had a squint and still wore glasses. He had just been seen by an ophthalmologist, who on a previous consultation had found only 3 per cent vision in the right eye, but now reported some improvement. The neurological examination was normal, EEG was normal. Psychological examination could not be carried out. —It was later reported that he had begun school at just under 7 years of age and made good progress.

Diagnosis: behaviour disorder convergent squint (familial).

No 73 (2265/3/1954)

A boy born in a private clinic at term on May 1 1954 to a primipara following a normal pregnancy. The delivery was prolonged. Stimulant injections were given.

but no morphia. The course was uncomplicated. The infant was asphyxiated for about 15 minutes and was given lobeline. Two hours after birth he was admitted to the DPGs with a diagnosis of congenital debility. On admission he exhibited flaccidity and grunting respiration, his colour was good except for harlequin colour change on its occasions. He made rapid recovery and was discharged after 4 days in apparently good condition.

Diagnosis: congenital debility

His growth and motor development were normal. He walked by the time he was one and his motor pattern was normal. His vision and hearing were good. He had a mild Aquist (familial). He talked at about 2-3 years; his mental development as felt to be normal, though he had a nervous disposition and was easily frightened. He also exhibited violent temper tantrums and there was nocturnal teeth grinding with decreasing frequency.

He was mentally and physically developed in line with his age, when seen at follow up at 4 years. His behaviour appeared normal during the examination. Neurological examination and EEG were normal.

Diagnosis: behaviour disorder, convergent aquist (familial).

No. 74 (9802/3/1954)

A boy born in a private clinic at term on Aug. 11 1954, to a multipara of 40 years (her last delivery had occurred 17 years earlier). The pregnancy was uneventful. Because the delivery did not progress, repeated stimulant injections were given. There is no record of the use of morphia. The course was otherwise normal. The cord was wound around the infant's neck. He was asphyxiated for a few minutes and was given lobeline. Within the first 24 hours he was admitted to the DPGs because of generalized convulsions. On admission his colour was good, but he was markedly rigid and during the second day of life again developed generalized tonic seizure. His tone quickly returned to normal and his condition thereafter was normal. He was discharged after 5 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

Re-examination at 3 months was recommended. However he failed to attend at that time.

His growth and motor development were satisfactory; he walked at one year. His vision, hearing and speech were normal. He talked adequately at 2-3 years. His mental development was satisfactory though he was markedly restless. His mother admitted to his being quite spoiled.

When seen on follow-up examination at four years his physical development was compatible with his age; though he seemed rather babyish, his intelligence was felt to be adequate. An EEG carried out one year later was normal. At that time he was still very fidgety and unstable. A psychological examination was suggested, but could not be carried out.

Diagnosis: behaviour difficulties.

No. 75 (403/3/1947)

A boy born in a private clinic at term on Aug. 31 1947 to a primipara following normal pregnancy. The delivery was prolonged, but apparently uncomplicated. No information is available concerning labour stimulation or morphia. BW was 4200 g. The cord was wound around the infant's neck, and he was asphyxiated for about 20 minutes, during which time he was given oxygen, artificial respiration, lobeline and cardiacol. He developed a generalized tonic convulsion and was immediately transferred to the DPGs with a diagnosis of tentorial tear. On admission he was rigid, and during the first 3 days of life he had several convulsions. His muscle tone gradually returned to normal and no other abnormal features were observed. He was discharged after 18 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth and motor development were good; he sat up at 6 months and walked

at 14 months. His motor pattern was normal but he was left-handed, (so was a half uncle). He had a squint, but his vision was good. He talked at about 2 years. His mental development was fairly satisfactory except for a difficult temperament particularly during his early years of life. He started school at the usual time, but had reading difficulties. During his second year in school the school-psychologist reported his intelligence to be normal. In the third year he was referred to a special reading class. He changed school three times during this year and the following one because of poor progress. From his 12th to 14th year he attended the Institute for Dyslectics. He gradually achieved good standard of reading, but still had trouble with writing. (The half-uncle mentioned above also was dyslectic).—He had nocturnal enuresis until the age of 10 years. (This was not a familial feature).

On follow-up examination, when 11 years of age, his physical development was normal for his age and mentally he appeared normal. There was a negligible squint. His motor development was normal apart from his left-handedness. The neurological examination was normal. EEG was not performed.

Diagnosis: familial (?) dyslexia, squint, previous nocturnal enuresis, left-handedness.

No 76 (664/3/1950)

A boy born in a private clinic at term on Oct. 8, 1950 to a primipara of 35 years, following a normal pregnancy. The delivery was very quick, but otherwise seems to have been uneventful. Labour stimulation as well as morphia was given. The infant was not asphyxiated. He was admitted to the DPGs 8 days old because of weight loss, the diagnosis being infantile atrophy. During the admission he was rather listless and sucked poorly but was otherwise normal. When discharged after 10 days he was still somewhat listless, but otherwise apparently normal.

Diagnosis: congenital debility

His growth as well as his motor and mental development were satisfactory. He walked normally at the age of one. His vision and hearing were normal. He said single words at one year and his speech was adequate by 2 years. After entering kindergarten at age 3 he began to stammer. This persisted, and from the age of six he was given speech therapy with some benefit. He started school at the usual time and his progress was good. He presented no behavioural problems, though he was easily frightened. He suffered from enuresis (non-familial).

He was followed-up at the age of 7 1/2, at which time his physical and mental development was compatible with his age. There was a negligible stammer. His speech was otherwise normal. The neurological examination was normal. EEG-examination was refused by the parents.

Diagnosis: stammer, enuresis.

No 77 (7466/3/1951)

A girl born at home at term on Aug. 6, 1951 to a multipara following a normal pregnancy. The delivery was uneventful. It was stimulated by one injection. There is no record of morphia being given. The infant was not asphyxiated. However she was admitted to DPGs during the first 24 hours because of an episode of generalized convulsions. She presented no other abnormalities and was discharged on the following day in apparently good condition.

Diagnosis: congenital debility

Her growth and development were satisfactory. She walked at one year. Her motor pattern, vision, hearing and speech were all normal. She talked at 2 years. She presented no behaviour problems, though she was said to be nervous and easily frightened and to have a nocturnal enuresis (which was familial). She started school at the normal time and did well.

On follow-up examination, aged 7 1/2, her physical development was compatible with her age. Mental development appeared normal. The neurological examination was normal.

Diagnosis: nocturnal enuresis (familial).

No. 78 (2263/3/1953)

A boy born at home at term on May 5, 1953 to a multipara, following normal pregnancy. The delivery was uncomplicated, labour stimulation and morphia were not given, but the delivery took place under full anaesthesia. The infant was asphyxiated for about 20 minutes, during which time he was given lobeline and nikethamide twice. He was immediately admitted to the DPGs with the diagnoses of asphyxia and asileptin. He was flaccid on admission and during the first day he developed an episode of generalized convulsions. He sucked poorly but recovered after a few days and was discharged after 6 days in apparently good condition.

Diagnosis: congenital debility nikethamide intoxication.

His growth was good and his mental and physical development satisfactory. He sat up at 7 months and walked at 15 months. His vision and hearing were normal. He talked before he was two years old. There were no behaviour problems. He had diurnal and nocturnal enuresis. When just under 5 years old he was admitted to children's hospital (Fogelballen). No urological abnormalities were found to explain the enuresis. The social conditions were considered unsatisfactory. Psychological testing was not performed. He appeared normally developed.

When seen at follow-up, just under 5½ years of age, his height was about average, he was well proportioned and well-nourished. His mental development appeared compatible with his age. The neurological examination was normal. An EEG had not been done.

Diagnosis: enuresis.

No. 79 (1667/3/1954)

A boy born in a private clinic at term on April 21, 1954, to a 32-year-old primipara following a normal pregnancy. The delivery was prolonged, but otherwise apparently normal. There is no report of labour stimulation but morphia was given. BW was 4600 g. The infant was not asphyxiated, but was admitted to the DPGs on the third day with diagnosis of dehydration and fever. He was sublethargic on admission (temp. 37.8 °C), and he was restless and sucked poorly. His temperature rose to 39.4, but on the same day again fell to 37 °C. He gradually sucked better and was discharged after 6 days in apparently good condition except for a doubtful rash (his toes had earlier been described as normal).

Diagnosis: intracranial haemorrhage, sequelae of difficult birth.

His growth as well as motor and mental development were satisfactory. He walked at 10 months. His vision and hearing were normal. A divergent squint was noted. (Squint runs in the family). He talked at 2 years. He presented no real behaviour problems, though he did not get on well with other children, preferring to be on his own, and he annoyed himself well. There was nocturnal teeth grinding.

At follow-up, when 4½ years of age, he was found to be well-developed physically and mentally. The neurological examination was normal. He was not yet dry at night (no family history of enuresis).

Diagnosis: nocturnal enuresis, familial squint.

A 80 (408 2/1949)

A boy born in private clinic at term on July 15, 1949, to a 34-year-old multipara, who during the first three months of pregnancy had suffered from severe vomiting and later developed oedema and possibly albuminuria. The membranes had ruptured some three days before delivery. Labour-stimulating injections were given (no record of morphia). Otherwise the course was apparently uneventful. BW was 4290 g. Asphyxia was not mentioned in the notes, but dicardamine was given. During the first 24 hours the infant developed cyanotic attacks and was transferred to the DPGs suspected of intracranial haemorrhage. He was flaccid and restless on admission, and during the following ten days exhibited several additional cyanotic attacks. Thereafter

he improved and presented no further abnormal features. He was discharged after 4 days in apparently good condition.

Diagnosis: suspected intracranial haemorrhage.

His growth as well as his motor and mental development were normal. He walked normally before the age of one year, talked at 2 years and started school at the normal time. There were no behaviour problems. He did well at school, but was thought to be dyslectic. However special teaching was not provided by the school. There were other cases of dyslexia in the family.

He was seen at follow-up when just under 9 years old. His physical and mental development then was found to be compatible with his age. The neurological examination was normal. EEG had not been performed.

Diagnosis: familial dyslexia (?).

No 81 (3535/3/1932)

A girl born in hospital (St. Lukas Stiftelsen) at term on May 28 1932, to a multipara following a normal pregnancy. The delivery was prolonged but otherwise apparently normal. Stimulant injections were given and forceps were applied. Morphine apparently was not given. The infant was asphyxiated for a few minutes, during which time oxygen and lobeline were given. She was transferred to the DPGs within the first 24 hours suspected of intracranial haemorrhage. Her temperature was raised (38 C). On admission she was flaccid, but otherwise normal. Her temperature fell to normal levels within the first 24 hours without any further rise. Her tone gradually became normal. She was discharged after 6 days in apparently good condition.

Diagnoses: intracranial haemorrhage, difficult birth.

Her growth and development were satisfactory. She sat and walked early, her vision and hearing were normal. She talked before the age of two. She started school when 6 years old and did well. She had had a drooping left eyelid since birth, which persisted unchanged. It was also noted that on exertion the left side of her forehead turned red, while the right side remained pale, with a sharp demarcation line. This prompted referral to the NPO of the RH when she was 4 1/2 years old. The examination revealed no neurological or other abnormalities except for the left sided ptosis. EEG was normal.

She was followed-up at 6 1/2 years. Her physical and mental development then appeared normal. There was a left sided ptosis, otherwise her facial movements were normal. Neurological examination was normal.

Diagnosis: left-sided ptosis.

No 82 (6571/3/1951)

A girl born in a private clinic at term on July 19 1951 to a multipara following a normal pregnancy. The delivery was prolonged, but apparently otherwise normal. It was stimulated by injection, but morphine was not given. There is no information concerning asphyxia, but lobeline was given. The infant was admitted to the DPGs immediately after birth with a diagnosis of congenital debility suspected heart disease, cyanosis. On admission she was flaccid and cyanotic, and her respiration was grunting. During the first 2 days she sustained repeated cyanotic attacks in spite of oxygen therapy. Thereafter she recovered and her respiration and tone gradually returned to normal. Chest X ray and auscultation gave no evidence of heart disease. She was discharged after 14 days in apparently good condition.

Diagnosis: atelectasis of the lungs.

Her growth and mental development were satisfactory. She walked at one year. Her hearing and speech were normal. She had a squint, which was treated by an occlusive eye patch and glasses. The visual acuity of the right eye nevertheless was greatly diminished (No family history of eye defect). Her behaviour was normal and she was expected to be ready for school at the usual time.

At follow-up, at 6 $\frac{1}{2}$ years, she was found to be developed mentally and physically in line with her age. She wore glasses, had mild convergent squint and impaired visual acuity in the right eye. The neurological examination was normal. EEG as not performed.

Diagnosis: convergent squint.

A. 43 (3558/205/1955)

A girl born in private clinic before term on May 16, 1955, to a primipara following normal pregnancy. The delivery was accompanied by a good deal of bleeding and slight separation of the placenta was demonstrated. Otherwise the course was normal. There is no record of labour stimulation or morphia. BW was 2300 g. Asphyxia is not recorded. During the first 24 hours the infant was admitted to the DPGs with diagnosis of prematurity congenital debility. On admission she was trembling and her respiration was grunting. During that day she sustained repeated cyanotic attacks. Her respiration improved within 24 hours and she gradually became more quiet. No other abnormal features were observed. She was discharged after 19 days in apparently good condition.

Diagnosis: suspected intracranial haemorrhage.

Her growth and physical development were satisfactory. She walked at one year. She had a convergent squint (which was familial feature); her vision was felt to be normal. Her hearing was adequate. She talked at about 18 months. Her mental development and behaviour were satisfactory.

On follow-up examination, aged 3 $\frac{1}{2}$ years, she was found to have developed physically and mentally according to her age. The neurological examination was normal. Her convergent squint persisted.

Diagnosis: (familial) convergent squint.

he improved and presented no further abnormal features. He was discharged after 4 days in apparently good condition.

Diagnosis: suspected intracranial haemorrhage.

His growth as well as his motor and mental development were normal. He walked normally before the age of one year talked at 2 years and started school at the normal time. There were no behaviour problems. He did well at school, but was thought to be dyslectic. However special teaching was not provided by the school. There were other cases of dyslexia in the family.

He was seen at follow-up when just under 9 years old. His physical and mental development then was found to be compatible with his age. The neurological examination was normal. EEG had not been performed.

Diagnosis: familial dyslexia (?).

No 81 (3535/3/1952)

A girl born in hospital (St. Lukas Stiftelsen) at term on May 28 1952, to a multipara following a normal pregnancy. The delivery was prolonged but otherwise apparently normal. Stimulant injections were given and forceps were applied. Morphine apparently was not given. The infant was asphyxiated for a few minutes, during which time oxygen and lobeline were given. She was transferred to the DPGs within the first 24 hours suspected of intracranial haemorrhage. Her temperature was raised (38 C). On admission she was flaccid, but otherwise normal. Her temperature fell to normal levels within the first 24 hours without any further rise. Her tone gradually became normal. She was discharged after 6 days in apparently good condition.

Diagnoses: intracranial haemorrhage, difficult birth.

Her growth and development were satisfactory. She sat and walked early. Her vision and hearing were normal. She talked before the age of two. She started school when 6 years old and did well. She had had a drooping left eyelid since birth, which persisted unchanged. It was also noted that on exertion the left side of her forehead turned red, while the right side remained pale, with a sharp demarcation line. This prompted referral to the NPO of the RH when she was 4 1/2 years old. The examination revealed no neurological or other abnormalities except for the left sided ptosis. EEG was normal.

She was followed-up at 6 1/2 years. Her physical and mental development then appeared normal. There was a left sided ptosis, otherwise her facial movements were normal. Neurological examination was normal.

Diagnosis: left sided ptosis.

No 82 (6571/3/1951)

A girl born in a private clinic at term on July 19 1951 to a multipara following a normal pregnancy. The delivery was prolonged, but apparently otherwise normal. It was stimulated by injection, but morphine was not given. There is no information concerning asphyxia, but lobeline was given. The infant was admitted to the DPGs immediately after birth with a diagnosis of congenital debility suspected heart disease, cyanosis. On admission she was flaccid, and cyanotic, and her respiration was grunting. During the first 2 days she sustained repeated cyanotic attacks in spite of oxygen therapy. Thereafter she recovered and her respiration and tone gradually returned to normal. Chest X-ray and auscultation gave no evidence of heart disease. She was discharged after 14 days in apparently good condition.

Diagnosis: atelectasis of the lungs.

Her growth and mental development were satisfactory. She walked at one year. Her hearing and speech were normal. She had a squint, which was treated by an occlusive eye patch and glasses. The visual acuity of the right eye nevertheless was greatly diminished. (No family history of eye defect). Her behaviour was normal and she was expected to be ready for school at the usual time.

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ACTA
PÆDIATRICA
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SUPPLEMENT 194 1969

STUDIES ON THE SERUM BINDING
OF VITAMIN B₁₂ IN THE
NEWBORN HUMAN INFANT

BY ANTTI KUMENTO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 191, 1960

*From The Hematology and Radiosotope Research Laboratories
Veterans Administration Hospital, Albany New York*

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by

Antti Kumpulainen

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This study was carried out in the Hematology and Radioisotope Research Laboratories of the Veterans Administration Hospital, Albany New York, during my research fellowship in the Department of Pediatrics, Albany Medical College of Union University Albany New York, from September 1966 through August 1967. My chief, Dr. Charles A. Hall, M.D., Professor of Medicine in Albany Medical College suggested me this study and made the performance of it possible. His wide knowledge and experience in the field of vitamin B₁₂ research, as well as his stimulating encouragement were of primary importance to me throughout this work.

The chief biochemist of our laboratory, Mr. Alexander E. Finkler, B.S., deserves my sincere thanks for his ever available assistance. His thorough knowledge and technical skills in the field of vitamin B₁₂ binders were essential for the performance of this study.

Dr. A. Leonardi Lubby, M.D., Professor of Pediatrics in New York Medical College and Chief Section of Hematology was one of the initiators of the present study. I am very grateful for the many stimulating discussions

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Miss Mary E. Rappazzo, M.S., deserves my most sincere thanks for nice and competent assistance. Mr. Edward S. Allen performed the vitamin B₁₂ assays. The drawings for this publication were made by the Medical Illustration Service of the Veterans Administration Hospital and partly by the Medical Illustration Service of Albany Medical College. Dr. Hall and Miss Rappazzo revised the language of my text.

The preparation of the manuscript was completed at the Children's Hospital of Turku University Finland. My thanks are due to my present chief, Professor Thomas Peltonen, M.D., who has given all his support to me during this work. I am grateful to Docent Ruth Wegelius, M.D. for valuable discussions.

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This work was supported in part by Grant A3102808 of the U.S. Public Health Service.

Turku, January 1968

Aulis Kumpulainen

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Turku, January 1969

Ilmari Kuusisto

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Abbreviations

B ₁₂	vitamin B ₁₂
IF	intrinsic factor
TC I	transcobalamin I
TC II	transcobalamin II
FTC	fetal transcobalamin
DEAE	diethylaminoethyl cellulose
CM	carboxymethyl cellulose

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DEAE	diethylaminoethyl cellulose
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Introduction

Several peculiarities in the metabolism of vitamin B₁₂ in the fetus and the newborn have been established by previous investigations

- There is a significant difference between maternal and fetal serum vitamin B₁₂ levels in favor of the fetus.
- There is an active transport process for vitamin B₁₂ across the placenta.
- The tissue vitamin B₁₂ concentrations in the fetus differ from the adult concentrations.
- The initially high serum vitamin B₁₂ concentration changes rapidly during the early weeks of life.
- There is an intrinsic factor independent

system for intestinal uptake of vitamin B₁₂ in the newborn rat.

The above listed features will be reviewed in detail in the following section.

The present study was undertaken to investigate whether any abnormalities in serum vitamin B₁₂ binding were connected to the peculiarities listed above. The principle was to label serum proteins with Co-vitamin B₁₂ *in vitro* and to fractionate the labeled serum by various methods in order to separate and characterize the vitamin B binders.

Part of the results were presented in a preliminary form before the National Meeting of the American Federation for Clinical Research in April 1967 (Luzumto *et al.* 1967).

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Part of the results were presented in a preliminary form before the National Meeting of the American Federation for Clinical Research in April 1967 (Kumanto *et al.* 1967)

Review of Literature

The following aspects of the metabolism of vitamin B₁₂ during pregnancy and the neonatal period have been studied

- serum vitamin B₁₂ levels during pregnancy
- the relationship between maternal and fetal serum B₁₂ concentrations at the time of delivery
- the transplacental passage of vitamin B₁₂ in rat guinea pig dog and man
- tissue concentrations of vitamin B₁₂ in the human fetus
- serum vitamin B₁₂ concentrations during early infancy
- the peculiarities in the intestinal absorption of vitamin B₁₂ in the newborn

The results of these studies will be reviewed. Additionally a brief review will be presented about the serum binding of vitamin B₁₂.

Concentration of vitamin B₁₂ in the serum of pregnant women

The first report about the serum B₁₂ concentrations during pregnancy is by Heinrich (1954). He studied the sera of 185 pregnant and puerperal women. Twenty percent of them had a lower than normal level of serum B₁₂ and simultaneously low urinary excretion of B₁₂. He attributed these phenomena to the increased need of B₁₂ caused by pregnancy. The work of Heinrich has been followed by a large number of investigations confirming the low levels of serum B₁₂ during pregnancy. Boger *et al* (1956, 1957a) demonstrated low serum B₁₂ levels in their study of 50⁹ pregnant women. They also demonstrated a direct and statistically significant correlation between serum level of vitamin B₁₂ and duration

of pregnancy. Other studies showing the decreased serum B₁₂ levels are *e.g.* those by Karlin (1955) Baker *et al* (1957) Young *et al* (1959) Hansen (1959) Lavigne *et al* (1960) Lowenstein *et al* (1960) and Ball and Giles (1964). Lowenstein *et al* also presented evidence for other factors besides hemodilution being responsible for the lowering of serum B₁₂ levels during pregnancy. Hellegers *et al* (1957) and Chow *et al* (1958) showed that pregnancy increases the intestinal absorption of vitamin B₁₂ both in man and in rat and thus supported the concept that an increased demand rather than a limited supply of vitamin B₁₂ is responsible for the observed low serum B₁₂ levels. Lohby *et al* (1961a) however found a decreased intestinal absorption of vitamin B₁₂ during the last few weeks of pregnancy in man. Young *et al* (1959) showed that rapid successive pregnancies cause a marked depression of maternal serum B₁₂ levels. Ball and Giles (1964) did not confirm this on their material.

Somewhat different results were obtained by Gotchel and Lovett (1960). They found declining serum B₁₂ concentrations during pregnancy with a sharp rise 4—6 weeks ante partum. Lawrence and Kilpatrick (1967) found low serum B₁₂ values in a group of anemic and non-anemic pregnant women. They retested 11 sera by the coated charcoal assay based on isotope dilution and found normal values in nine of the retested sera. The authors suggested that serum B₁₂ values in pregnant women may in fact be normal and the low values obtained by microbiological assays may be caused by some inhibitory agent. The eleven above cases are the only reported pregnant women tested by other

than microbiological methods, and obviously more work is needed to clarify this aspect. Sullivan *et al.* (1967) were not able to demonstrate any decrease in the serum B₁₂ concentration during pregnancy using a microbiological assay.

The capacity of serum to bind added B₁₂ has been reported to be increased during pregnancy (Przyrowsky *et al.* 1959 Sadovsky *et al.* 1959, Lowenstein *et al.* 1960, Sullivan *et al.* 1967).

The difference in serum concentration of vitamin B₁₂ between mother and fetus

Killander and Wahlqvist (1954) were the first ones to report the difference in serum B₁₂ concentration between mother and fetus. This transplacental concentration gradient in favor of the fetus has been confirmed by a large number of investigations, e.g. Karlin and Dumont (1956) Okuda *et al.* (1958) Hoyer *et al.* (1957a, 1957b) Dumont and Karlin (1957) Dixit *et al.* (1957) Killander (1957) Baker *et al.* (1958) Przyrowsky *et al.* (1959) Sadovsky *et al.* (1959) Lowenstein *et al.* (1960) Lohby *et al.* (1961a, 1961b) and Zachau-Christiansen *et al.* (1962). In the serum of Zachau-Christiansen *et al.* the average maternal serum B₁₂ concentration was 40 pg/ml and cord serum B₁₂ concentration 70 pg/ml, whereas Lohby *et al.* (1961b) reported values of 177 pg/ml and 331 pg/ml for maternal and cord serum, respectively. Both groups used a modification of the *Lactobacillus lactis* assay.

There is one situation where fetal B₁₂ level as judged by cord serum, has been reported to be exceptionally low. Okuda *et al.* (1958) Hellegers *et al.* (1957) and Chow and Okuda (1961) gave reports on four cases of congenital twins who all had very low levels of serum B₁₂ at birth. They had no knowledge of congenital erythraemia with normal serum B₁₂ concentrations at birth.

The transplacental passage of vitamin B₁₂

The studies referred to in the previous chapter already indirectly show that there is an active transport of B₁₂ across the placenta producing the transplacental concentration gradient of vitamin B₁₂ in favor of the fetus. There is also direct experimental evidence for such a phenomenon.

Chow *et al.* (1951) injected relatively large amounts of radioactive vitamin B₁₂ into pregnant rats and measured the radioactivity in the offspring. They detected a total of 18% of the injected dose in the fetuses and in the placentas, whereas amniotic fluid was free from radioactivity. Karlin (1956, 1957) studied the distribution of vitamin B₁₂ after oral and parenteral administration to pregnant guinea pigs. She found an accumulation of vitamin B₁₂ in both maternal and fetal tissues and in the placenta. Hellegers *et al.* (1957) performed elegant studies feeding or injecting small doses of radioactive vitamin B₁₂ to pregnant rats. They observed that about 60% of the radioactivity passed to the fetuses and much less radioactivity accumulated in the maternal organs when compared to nonpregnant rats treated similarly. Rice *et al.* (1958) obtained the same kind of results using huge doses of radioactive vitamin B₁₂.

Lohby *et al.* (1958, 1959a, 1961a) studied the placental transfer of vitamin B₁₂ in rats using tracer amounts of C¹⁴-labeled B₁₂. Their results showed that B₁₂ administered at the end of pregnancy first built up in the placenta for the first two days and then gradually passed to the fetal side over a 3-week period, to a maximum transfer of 33–45% of the administered dose. 1–5% of the dose remained in the placental tissue. They were also able to show that only newly administered B₁₂ was available for placental transfer. Radioactive B₁₂ which was present in the maternal liver from the time before

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compared to fetuses at a similar stage of development. It is thus possible that a severe enough maternal B_{12} deprivation leads to fetal death.

Saastamöki *et al.* (1961) dealt with an other type of disturbed maternal B_{12} metabolism. In their material the mothers had exceptionally high serum B_{12} levels due to malabsorptive liver disease. Even then, the cord serum B_{12} levels were generally higher than the maternal levels.

Fetal tissue concentrations of vitamin B_{12}

The vitamin B_{12} concentrations in human fetal tissues have been studied by Killander (1958) and extensively by Salmi (1963). The concentrations were found to be at the same levels during the studied period of intrauterine life with the exception of the central nervous tissue where a declining trend was noticed with advancing maturity. According to Salmi, the highest concentration was represented by the kidneys, the adrenal gland, and the liver followed by the thyroid gland. He noticed further that the tissue B_{12} levels in the same fetus were throughout high or low and attributed this to the maternal supply of vitamin B_{12} to the fetus.

Neither Killander nor Salmi published adult tissue B_{12} levels for comparison. There are many studies by different investigators of the adult B_{12} tissue concentrations, human liver especially has been extensively studied. A brief review concerning adult tissue B_{12} concentrations were presented *e.g.* by Salmi (1963) and by Ståhlberg *et al.* (1967). Direct comparisons between the results from different laboratories are not reliable especially when dealing with such a complicated test as the determination of tissue B_{12} concentration. However, if one compares the results of Salmi to the unpublished results of Hall (1967) it seems obvious that the fetal liver has lower B_{12} concentration than the adult

liver whereas other fetal concentrations are either higher or the same as adult concentrations.

To overcome the difficulties in comparing results from different laboratories, Rappazzo *et al.* (1968) undertook a study on this subject. Their results showed that the B_{12} concentration in fetal liver is lower than that in adult liver. Various levels of significant differences were also found in comparing fetal and adult kidney, spleen, heart, lung, brain and colon. The B_{12} concentration in fetal thyroid was higher than the adult concentration, this difference was significant at the 5% level. The other tissue B_{12} concentrations were at about the same levels in adults and fetuses.

As to the liver it is not surprising to find a low B_{12} concentration in the fetus. The liver is functionally immature at birth (reviewed *e.g.* by Schellong 1962) and its gross circulation, as well as the circulation at the arteriole level is different from the adult circulation (Järvelä 1964). Thus the low B_{12} concentration probably reflects the state of the liver more than the peculiarities in the metabolism of vitamin B_{12} .

On the other hand, the thyroid gland is known to be metabolically active at birth. This was confirmed *e.g.* by Peltonen and Hänninen (1964, 1965) who discovered the rapid recovery of high infant protein-bound iodine values after the transient lowering by exchange transfusions. Another interesting correlation is that reported by Chow and Okuda (1960) namely the low serum B_{12} values in congenital cretina. This correlation was discussed *e.g.* by Salmi (1963). The relationship between these two co-existent phenomena is unexplained so far.

The serum B_{12} concentrations during early infancy

Luhbr *et al.* (1961b) followed the serum concentrations of vitamin B_{12} during early

conception was not at all transferred to the fetus.

Luhby *et al* (1959b) and Woods *et al* (1960) studied the transplacental passage of vitamin B₁₂ in dog and confirmed the transfer of B₁₂ from the maternal circulation to the fetus through the placenta. Danesino and Montumagno (1961) studied the same situation in guinea pigs. Their observation period was only 15 minutes after an intravenous injection of B₁₂ during which short time the administered B₁₂ started to accumulate in the placenta but did not pass to the fetal side.

Salmi (1963) studied the fetal distribution of labeled B₁₂ injected into pregnant rats. He found the maximum concentrations of labeled B₁₂ in fetal kidney, liver, adrenal and thyroid gland. The distribution of nonradioactive B₁₂ was found to be the same as to the order of concentration.

There is thus ample evidence about the placental transfer of vitamin B₁₂, and even the mode of transmission has been clarified to some extent in the investigations cited above. Analogous situations of the transplacental concentration gradient of vitamin B exist even for some other vitamins and iron. Chow and Okuda (1960) studied fetal and maternal serum concentrations of vitamin C, vitamin B₆, and iron all of which were in higher concentrations in the fetus. The transplacental concentration gradient of serum folic acid in favor of the fetus was demonstrated e.g. by Baker *et al* (1958), Zachau-Christiansen *et al* (1962) and Giles (1966). Zachau-Christiansen *et al* also confirmed the concentration gradient for serum iron. Wöhler (1964) studied the metabolic phenomena in the transport of iron through the placenta. Råjhä (1958) published an extensive experimental study on the placental transfer of vitamin C. Lust *et al* (1954) presented a detailed model for the transplacental passage of riboflavin against a concentration gradient. It is thus obvious that the transplacental concentration gradient and active placental

transport of vitamin B₁₂ are not unique. They rather reflect a common feature in the placental function.

The effect of maternal B₁₂ deficiency on the fetus

There are several animal studies concerning the untoward effects of severe maternal B₁₂ deficiency on the fetus (e.g. Lepkovsky *et al* 1951, Jones *et al* 1955). Neabitt and Chow (1958) presented a general review of the earlier studies. Woodard and Newbame (1967) reviewed the literature and reported a detailed study concerning the pathogenesis of hydrocephalus in the offspring of B₁₂ deficient rats.

Salmi (1963) studied the phenomenon in a more physiologic manner producing only marginal B₁₂ deficiency in rats. A low vitamin B₁₂ diet for the dam distinctly lowered the fetal tissue concentrations of B₁₂. The lowering was most manifest in the brain tissue and a sharp decline was noticed in the kidney whereas the decrease in concentration was least in the liver.

The information concerning the effects of B₁₂ deficiency on developing human fetus is scanty. Baker *et al* (1962) studied nine untreated B₁₂ deficient delivering mothers and their infants in India. All the mothers were frankly B₁₂ deficient by several criteria. Seven of them gave birth to healthy full term infants. Interestingly the cord serum B₁₂ levels of these infants were markedly higher than the maternal serum B₁₂ levels, although lower than reported for cord serum by other investigators. Only one of the seven infants had intermediate megaloblasts in the bone marrow. Thus, the fetus seems to be able to get its share of vitamin B₁₂ even when the mother is in a state of deficiency. Two of the mothers delivered stillborn premature fetuses. Their liver content of vitamin B₁₂ was analyzed and found to be distinctly lower as

suggested different functions in the process of B_{12} transport for the different binding sites. Later on they were able to clearly separate the "early stage binder" from the previously known globulin B_{12} binder (Hall and Finkler 1963). In a study on the dynamics of the B_{12} binders (Hall and Finkler 1964) the current nomenclature for the binders was introduced and their properties and functions were described and discussed. The trace plasma protein which bound vitamin B_{12} after parenteral or oral intake was isolated and designated transcobalamin II (TC II). Its behavior on DEAE- and CM-cellulose chromatographies was studied, and it was shown to have β -globulin mobility in electrophoresis. Labeled B_{12} bound to TC II disappeared rapidly from the circulation. It was concluded that the function of TC II is transport system for the phase of B_{12} metabolism immediately after intake. The other B_{12} binder the carrier of endogenous B_{12} was found to bind little of the added B_{12} . It was designated TC I. The B_{12} bound to it had a much slower turnover.

Subsequently Hall and Finkler (1966a) studied the serum binding of *in vivo* added B_{12} . The binding corresponded to the pattern found immediately after *in vivo* administration of the vitamin with main binding to TC II and little binding to TC I. When large amounts of B_{12} were added, other proteins besides TC II and TC I participated in the binding. These were considered to be nonspecific binders.

Looper and Larnach (1961) showed that mouse ascites fluid and human serum produced a twenty fold increase of uptake of vitamin B_{12} by mouse ascites tumor cells and by Hela cells. Finkler and Hall (1967) studied the same phenomenon using isolated B_{12} binders. Analogous to their *in vivo* observations, TC II was found to promote the uptake of B_{12} by human normal and malignant cells, whereas neither TC I nor the other studied binders (from erythrocytes,

leukocytes, saliva, and gastric juice) enhanced the uptake of B_{12} by the cells *in vitro*. Additionally evidence was obtained for TC I being an exit carrier for cell vitamin B_{12} .

Hotief *et al.* (1967a) described two serum B_{12} binders which they called α -binder and β -binder. The former corresponds to TC I and the latter to TC II. Their group also studied the relation of the binders to the uptake of vitamin B_{12} by reticulocyte-rich erythrocytes (Hotief *et al.* 1967b). They found the β -binder to deliver more B_{12} to erythrocytes than the α -binder.

An important contribution to the present knowledge about serum B_{12} binders comes from Hom and his co-workers. Hom *et al.* (1968) fractionated *in vivo* labeled serum by various methods and confirmed the earlier results of Hall and Finkler. The molecular weights for serum B_{12} binders were determined by Hom and Olesen (1967) using Sephadex gel filtration. A mean value of 13,000 was obtained for TC I and 38,000 for TC II. Hom (1967a) gave important information concerning the behavior of TC II *in vitro*. He demonstrated that TC II complexes and binds to Sephadex at low ionic strength. The resulting TC II complex has a molecular weight of over 200,000. A well designed study on the plasma turnover of $^{57}\text{CoB}_{12}$ bound to TC I and TC II was published by Hom (1967b). He showed that the labeled transcobalamins were diluted into a volume which was 2.3–3.1 times larger than the plasma volume. The half life of TC II $^{57}\text{CoB}_{12}$ complex was 1.5 hours and that of TC I $^{57}\text{CoB}_{12}$ complex 0.3 days. When $^{57}\text{CoB}_{12}$ -TC II was injected intravenously the label appeared bound to TC I in four hours after the injection, and was completely in that form 94 hours after the injection. The removal of TC II $^{57}\text{CoB}_{12}$ reported by Hom is slower than that given by Finkler and Hall (1967); this can be explained by the use of different points of time for analyzing the disappearance curve.

infancy. Their mean value for the cord serum B₁₂ concentration was 951 pg/ml, the value remained high for the first week and then rapidly decreased to an average of 312 pg/ml by one month. Further gradual decline to 228 pg/ml occurred by 6–7 months, followed by a slow rise to 403 pg/ml by 24–36 months of age. The results reported by Bar-Shany and Herbert (1967) are in agreement with those of Luhby *et al* cited above.

The intestinal absorption of vitamin B₁₂ in the newborn

Boness and Wilson (1964) studied the mechanism of intestinal uptake of vitamin B₁₂ in newborn rats. The intestine from fetal and newborn rats showed extremely high uptake of the vitamin in the absence of intrinsic factor (IF). The stomach wall of fetal and newborn rats contained less than 1% of the IF found in the adult rat. After the first week of life the amount of IF increased rapidly and simultaneously the IF independent uptake system decreased in activity. Newborn guinea pigs showed little uptake of B₁₂ in the absence of IF. The authors suggested that the phenomenon in newborn rats may be connected with their ability to absorb large protein molecules by pinocytosis. The timing of the phenomena is the same and neither of them is found in the guinea pig. An interesting discussion concerning this subject is presented in connection with an article by Wilson (1966).

Salmi (1966) studied the absorption of labeled B₁₂ from the digestive canal of guinea pig fetuses and newborn animals. He did not find any increase in the absorptive capacity during the development.

Little is known about the intestinal absorption mechanism of B₁₂ in the newborn human infant. Luhby *et al* (1958) fed tracer doses of ⁶⁰CoB₁₂ to newborn infants and reported an absorption of 75–90% whereas pregnant

women absorbed only 27–70%. Agunod *et al* (1967) from the same laboratory studied the intrinsic factor secretion in newborn infants and found little biological IF-activity during the first week of life. According to these two studies, an IF independent mechanism for B₁₂ absorption cannot be excluded. There are however divergent views on the presence of IF in newborn human infants. Bar-Shany and Herbert (1967) and Goldberg *et al* (1967) using different methods than Agunod *et al* concluded that intrinsic factor is present in the gastric juice of newborn infants.

The binding of vitamin B₁₂ by serum proteins

Pitney *et al* (1954) found the vitamin B₁₂ in serum to be mainly bound with proteins in the α -globulin electrophoretic fraction. This finding has since been confirmed by several investigators, e.g. Mendelsohn *et al* (1958), Weinstein *et al* (1959), Banerjee *et al* (1963) and Hardwicke and Jones (1966). A detailed review of the earlier studies was presented by Simons (1964). The B₁₂ binding protein in serum was shown to be an α -globulin and a constituent of the serum mucoid fraction.

Miller (1958) presented experiments showing the different mode of serum binding for *in vitro* added B₁₂ when compared to native or endogenous B₁₂. He found the added B₁₂ bound mainly with a β globulin. This difference has since been confirmed by various methods (Miller and Sullivan 1959a, 1959b, Simons 1964, Gabuzda *et al* 1965).

This duality in the binding of vitamin B₁₂ by serum proteins was clarified by the work of Hall and Finkler. In a study using intravenous administration of labeled B₁₂ they showed the binding of B₁₂ in more than one plasma fraction (Hall and Finkler 1962). The rate of B₁₂ disappearance from each fraction was different so that the plasma binding pattern changed with time. This

suggested different functions in the process of B_{12} transport for the different binding sites. Later on they were able to clearly separate the "early stage binder" from the previously known globulin B_{12} binder (Hall and Finkler 1963). In a study on the dynamics of the B_{12} binders (Hall and Finkler 1964) the current nomenclature for the binders was introduced and their properties and functions were described and discussed. The trace plasma protein which bound vitamin B_{12} after parenteral or oral intake, was isolated and designated transcobalamin II (TC II). Its behavior on DEAE- and CM-cellulose chromatographies was studied, and it was shown to have β -globulin mobility in electrophoresis. Labeled B_{12} bound to TC II disappeared rapidly from the circulation. It was concluded that the function of TC II is

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The vitamin B₁₂ binding capacities of serum transcobalamins were studied by Hom and Ahluwalia (1968), using *in vitro* labeling and Sephadex G 200 gel filtration for the separation of the binders. TC I bound up to 47.1 % of the added B₁₂ with a range from 8.5 to 47.1 % or from 72 to 1057 pg/ml, in different individual sera. TC II bound from 850 to 1891 pg/ml accounting for up to 90.3 % of the unsaturated binding capacity. The authors also abruptly introduced a third, large-sized binder termed TC 0. It was found to bind from 0 to 70 pg/ml accounting for up to 5.2 % of the serum unsaturated B₁₂ binding capacity. TC 0 I and II were the only binders of B₁₂ over the studied range from 75 to 20 760 pg/ml. There was an excess of II when large amounts were added and this excess remained unbound. The relative amounts of B₁₂ bound to TC I and to TC II remained fairly constant in individual sera regardless of the amount of B₁₂ added. The authors did not observe anything like the phenomenon of secondary binding described by Hall and Finkler (1966a) when large amounts of B₁₂ were added. A possible explanation for this difference is that the secondary binding observed by Hall and Finkler is a loose form of binding of low avidity. This bond may have loosened in the system used by Hom and Ahluwalia.

There is experimental evidence for the *in vitro* transfer of vitamin B₁₂ from intrinsic factor to TC II in the mouse (Tan and Hansen 1966). It was demonstrated in the mouse that 5–8 hours are needed after the *in vivo* saturation of TC II before serum desaturated TC II reaches normal values. Puromycin and cycloheximide inhibited the reappearance of desaturated TC II (Tan *et al.* 1967). It was further demonstrated by another technique that puromycin and cycloheximide cause a decrease of TC II in the mouse (Salhi *et al.* 1967). Rat liver perfusion experiments showed that TC II is produced in the liver (Haught *et al.* 1967).

Abnormalities in serum B₁₂ binders have been described in four situations.

— In chronic myelogenous leukemia, the serum concentration of B₁₂ is high and the unsaturated B₁₂ binding capacity is increased. The binding capacity of TC I has been shown to be greatly increased and the binding to TC II is diminished or nil (Beard *et al.* 1954, Miller 1958, Mendelsohn *et al.* 1958, Miller and Sullivan 1959a, 1959b, Weinstein *et al.* 1959, Banerjee *et al.* 1963, Hall and Finkler 1964, 1966b, Hom *et al.* 1966, Retief *et al.* 1967b, Mikkonen *et al.* 1967).

— In polycythemia vera, a special B₁₂ binding protein was described by Hall and Finkler (1967).

— In untreated pernicious anemia, the binding of added B₁₂ to TC II was shown to be diminished or even absent in some cases (Hall and Finkler 1966b, Lawrence 1966). Gräsbeck (1967) confirmed that TC II is not absent in pernicious anemia. The CoB₁₂ plasma clearance studies in B₁₂ deficiency support the view of abnormal B₁₂ binding (Hall *et al.* 1962, Hall and Finkler 1962, Moyer *et al.* 1967). All the above cited abnormalities change towards normal following the correction of B₁₂ deficiency.

— In pernicious anemia patients treated with long-acting B₁₂ preparations, high serum B₁₂ levels and elevated serum vitamin B₁₂ binding capacities were found. This was attributed to the presence of circulating IgG antibodies against TC II causing delayed plasma clearance of TC II B₁₂ complex (Schwartz and Bastrup-Madsen 1968, Olsen *et al.* 1968, Hom *et al.* 1968).

An extensive systematic study of B₁₂ binders in human body fluids and blood cells was published by Simons (1964). B₁₂ binding protein in human milk was studied by Finkler *et al.* (1967). A fascinating discussion concerning body B₁₂ binders and their relations to each other including phylogenetic speculations, was presented by Gräsbeck (1967).

Material and Methods

Serum

Cord blood was collected from the placental parts of umbilical cords immediately after normal deliveries at the Albany Medical Center Hospital, Albany, N.Y. Ten fifteen ml of blood as taken from one placenta. The serum as separated by gentle centrifugation within four hours. It was either refrigerated for not more than 24 hours prior to use or frozen immediately after separation and stored at -20°C until used. V. mildly hemolyzed samples are used. To check the possible effects of hemolysis, some grossly hemolytic serum samples are studied by DEAE-chromatography and no differences attributable to hemolysis are found.

The samples were collected from 23 normal deliveries, occurring at daytime between October 23, 1966 and June 14, 1967. Eleven of the babies were boys and 12 girls. Their birth weights ranged from 2520 to 4490 grams, the average birth weight in the series being 3370 grams.

Large scale preparative studies were performed on pooled serum from the above mentioned cord serum samples and on cord serum obtained from Grand Island Biological Corporation, Grand Island, N.Y. (catalog number 619). This specially ordered serum as prepared in the cold, immediately frozen, shipped in the frozen stage and stored at -20°C until used. The serum as delivered in 20 ml and 50 ml lots.

Infant blood was collected at the Flower and Fifth Avenue Hospital, New York, N.Y. Three serial samples are obtained from three healthy infants at different time intervals but one 1 day and 30 day.

Adult blood samples were collected from five healthy infants and from eleven infants hospitalized at the Flower and Fifth Avenue Hospital for various non-hematological disorders. Their ages are between 1 day and 1.5 day at the time of blood collection. The sera are separated and preserved as described above.

Maternal blood as obtained from the mothers of seven of the above mentioned healthy infants. The maternal blood was drawn the day after the delivery. Additionally blood as obtained from 1 healthy woman 11 weeks later at the Albany Medical Center Hospital, right before delivery. The maternal samples

are processed and stored identically with the infant and cord blood samples.

Normal adult blood was obtained from subjectively healthy male and healthy non-pregnant female laboratory personnel. Serum was separated and stored as above.

Vitamin B₁₂

The radioisotopic vitamin B₁₂ used in this work was ^{57}Co -labeled cyanocobalamin (B.P.). It was purchased from the Radiochemical Centre, Amersham, Buckinghamshire, England, through Merck and Co. Inc., Rahway, N.J. Three batches with the code CT-EP are used.

Batch 37, specific activity 45 $\mu\text{Ci}/\mu\text{g}$ on July 20, 1966. According to the manufacturer the radiochemical purity of the batch was 93% by distillation and electrophoretic analysis.

Batch 49, specific activity 70 $\mu\text{Ci}/\mu\text{g}$ on January 4, 1967. Radiochemical purity 95%.

Batch 61, specific activity 110 $\mu\text{Ci}/\mu\text{g}$ on July 22, 1967. Radiochemical purity 95%.

Aqueous dilutions, prepared from the above batches, as working solutions with suitable concentrations of Haman B₁₂. These working solutions were kept in the dark at $+4^{\circ}\text{C}$ and not used for more than one month after the dilution.

The non-radioisotopic vitamin B₁₂ used in this work was USP reference standard nonradioactive cyanocobalamin.

The measurement of radioactivity

The measurement of radioactivity was done by scintillation spectrometry. A well type crystal detector connected to a scintillation spectrometer (Beckman Model 550) with an automatic sample changer was used. The radioactivity of the samples was calculated using ^{57}Co standards of corresponding volumes. Counts per minute (cpm) for the standards were recorded daily and their actual radioactivity calculated using half life of 273 days for ^{57}Co . The counting efficiency of the system was 11×10^4 cpm/ μCi . The background varied between 20 and 40 cpm. A correction

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B₁₂ binders

All the ⁵⁷CoB₁₂ labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioactive vitamin B₁₂ added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B₁₂-binding capacity of serum proteins (*e.g.* Miller 1938). The working solutions of ⁵⁷CoB₁₂ contained 300 pg in 0.14–0.21 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking. After incubating in a +37°C water bath for 90 minutes, the serum sample was dialyzed against the starting buffer of the next procedure to remove any unbound B₁₂ and to equilibrate the sample. The serum sample was counted for radioactivity prior to and after the dialysis. Also the dialysing fluid was counted and no radioactivity could be detected in it when the standard amount of ⁵⁷CoB₁₂ was added.

The labeled serum was then submitted for various procedures in order to fractionate the vitamin B₁₂ binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ion exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co, Keene, N.H. The capacity of the cellulose was 0.9 meq/g. The new cellulose powder was suspended in water stirred and allowed to sediment. The yellowish supernatant containing the finest particles was decanted off. This was repeated twice. The cellulose was then suspended in 0.5 N NaOH and stirred for 20–30 minutes. The alkali was washed off with water until the pH of the washing water reached 7.0. The same treatment was repeated with 0.5 N HCl and then again with 0.5 N NaOH. When the last alkali had been washed off the cellulose was suspended in 0.01 M phosphate buffer pH 8.0 and the pH of the mixture brought to 8.0 with 0.3 M NaH₂PO₄. The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphate buffer and suspended in it. The pH was again checked and readjusted, if necessary. Two-three drops of toluene per 1 liter of the mixture was added as preservative. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A-50 capacity 3.9 meq/g made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia Fine Chemicals, Piscataway, N.J. It was processed as before

using 0.5 N acid and alkali, and suspended in 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Finkler (1965). Two modifications of the chromatography technique were used. The so-called mini-column technique was used to study the B₁₂ binding pattern of small serum samples, in the range of 1 ml. Columns with an internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0.01 M phosphate buffer pH 8.0. The packing was performed in 3–4 steps, first by gravity and then by applying an air pressure of ten pounds on the column. The final length of the column was 3 m. The labeled, dialyzed serum sample was layered on the column and washed in with the starting phosphate buffer. A concave phosphate buffer gradient of increasing molarity and decreasing pH, as modified by Hall and Finkler (1965) after Peterson and Chisare (1963) was used to elute the column. To produce the gradient a nine-chambered, continuous flow device was used. The starting buffer was 0.01 M pH 8.0 and the limiting buffer 0.3 M pH 4.5. The volume of each chamber was 0.3 ml. The flow rate in different columns varied between 0.5–7.0 ml/hr without any effect on the separation. Fractions of 5 ml were collected and assayed for protein and radioactivity content. The fractions from these small columns were not used for further separation or characterization of the B₁₂ binders.

The so-called "big column" technique of DEAE chromatography was used to process large amounts of labeled serum for further processing by other methods. DEAE-cellulose was packed to the height of 90 cm in columns with an internal diameter of 4 cm. The packing was performed in 4–5 steps, first by gravity and then by 10 pound air pressure. Up to 50 ml labeled serum was processed with these columns. The elution gradient was the same as described for "mini-columns" the volume of each chamber being 300 ml. The experiment was performed at a temperature of +4°C with a flow rate of 30–40 ml/hr. Fractions of 30–40 ml were collected and aliquot taken for protein, radioactivity and B₁₂ assay. The fractions were pooled according to the radioactivity distribution, concentrated by ultrafiltration and dialyzed for subsequent procedures.

CM-cellulose chromatography

Carboxymethyl (CM) ion exchange cellulose (Whatman column media CM 11 made in England by W & R Balston Ltd., nominal capacity 0.6 meq/g) was washed successively with ten times of 0.5 N HCl and 0.5 N NaOH. The acid and alkali were

altered off 11h after the added cellulose as compared to 0.01 M sodium chloride-sodium acetate buffer pH 5.4 and the pH of the mixture adjusted to 5.4. Thereafter the cellulose was stirred several times. The also contained acetate buffer resuspended in it and stored at +4°C. No need CM cellulose as employed.

A slurry of the cellulose in 0.01 M acetal buff r pH 5.4 as poured into column 11h an internal diameter of 1.5 cm and allowed to settle by gravity to the height of 45 cm. The sample which had been dialyzed against the same acetal buffer was layered on the column and washed in. The first elution as performed with 0.01 M acetate buffer pH 5.4 followed by 0.027 M phosphate buffer pH 7.8, and completed with 0.3 M phosphate buffer pH 7.8. The outlet of the column as connected to UV-sensor which indicated the location of the protein fractions. The buffer was changed after the location of protein peak.

The flow rate as kept at 60-65 ml/hr and fractions of 14 ml were collected and counted for radioactivity. The fractions were pooled according to the radioactivity peaks and concentrated for further use.

Gel filtration on Sephadex G

Sephadex G 200 made by Pharmacia, Uppsala, Sweden, as purchased from Pharmacia Fine Chemicals, Division of Pharmacia & Upjohn Co., Kalamazoo, Michigan, U.S.A. The buffer used in the gel filtration experiments as 0.01 M phosphate buffer pH 7.4 made 0.5 M for NaCl and contained 0.02 M sodium acetate as preservative.

The gel allowed to settle in the buff for 72 hours prior to use. A slurry of it as poured to the height of 70 cm in a glass column with an internal diameter of 2.5 cm. The column as stabilized with the buffer for 6 hours. The same column was used repeatedly.

The dialyzed sample (about 1-3 ml) as gently introduced on the column, allowed to enter and washed in. It then came 1 ml of the gel buffer. The column as kept with the gel buffer at flow rate of 4-15 ml/hr. The outlet of the column was run through photometer records of the absorption at 280 mμ. Fractions of 3 ml were collected and counted for radioactivity. Either the UV records or manual count as employed to determine the protein concentration.

The molecular weight estimations from the gel filtration experiments are based on the linear correlation between the elution volume of molecule and its logarithm of molecular weight (Andrew 1964). The amount of buff needed to let the peak

fraction was taken as the elution volume of the protein. The old column for the column was measured equally with Blue Dextran 2000 (Pharmacia). In order to eliminate the effect of possible alterations in the column during prolonged use the ratio of elution volume to old column as used instead of elution volume alone.

The following set of reference proteins (from Mann Research Laboratories Inc. New York, N.Y.) was used to produce the standard line illustrated in figure 1.

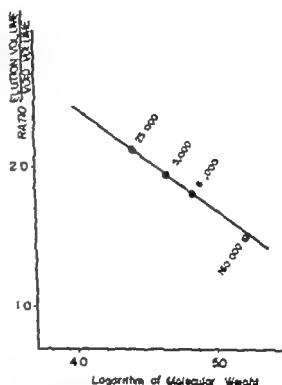


Fig. 1. The standard line used for molecular weight estimations by Sephadex G 200 gel filtration.

- ~ Chymotrypsinogen, molecular weight 25,000
 - ~ Ovalbumin, molecular weight 45,000
 - ~ Bovine albumin, molecular weight 67,000
 - ~ Human gamma globulin, molecular weight 160,000
- This standard line was used to estimate molecular weight also for the filtrated samples.

Sephadex G-100 was treated similarly as G 200 and column with the dimensions of 2.4 x 1.5 cm was prepared. This column was used to fractionate 1-3 ml samples of dialyzed serum. The protein distribution pattern recorded by the absorption at 280 mμ was used as reference to the location of the radioactivity peaks. No molecular weight estimations were performed on this column.

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B₁₂ binders

All the ⁵⁷CoB₁₂ labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioactive vitamin B₁₂ added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B₁₂ binding capacity of serum proteins (*eg* Miller 1938). The working solutions of ⁵⁷CoB₁₂ contained 300 pg in 0.14–0.1 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking. After incubating in a +3 °C water bath for 20 minutes, the serum sample was dialyzed against the starting buffer of the next procedure, to remove any unbound B₁₂ and to equilibrate the sample. The serum sample was counted for radioactivity prior to and after the dialysis. Also the dialysing fluid was counted and no radioactivity could be detected in it when the standard amount of ⁵⁷CoB₁₂ was added.

The labeled serum was then submitted for various procedures in order to fractionate the vitamin B₁₂ binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ion exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co, Keene NH. The capacity of the cellulose was 0.9 meq/g. The new cellulose powder was suspended in water stirred and allowed to sedimentate. The yellowish supernatant containing the finest particles was decanted off. This was repeated twice. The cellulose was then suspended in 0.5 N NaOH and stirred for 30–35 minutes. The alkali was washed off with water until the pH of the washing water reached 9. The same treatment was repeated with 0.5 N HCl and then again with 0.5 N NaOH. When the last alkali had been washed off the cellulose was suspended in 0.01 M phosphate buffer pH 8.0 and the pH of the mixture brought to 8.0 with 0.3 M NaH₂PO₄. The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphate buffer and suspended in it. The pH was again checked and readjusted, if necessary. Two-three drops of toluene per 1 liter of the mixture was added as a preservative. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A 50, capacity 3.9 meq/g, made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia Fine Chemicals, Piscataway N.J. It was processed as also

using 0.5 N acid and alkali, and suspended in 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Flinker (1965). Two modifications of the chromatography technique were used. The so called "mini-column" technique was used to study the B₁₂ binding pattern of small serum samples, in the range of 1 ml. Columns with an internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0.01 M phosphate buffer pH 8.0. The packing was performed in 3–4 steps, first by gravity and then by applying an air pressure of ten pounds on the column. The final length of the column was 3 cm. The labeled dialyzed serum sample was layered on the column and washed in with the starting phosphate buffer. A concave phosphate buffer gradient

of increasing molarity and decreasing pH, as modified by Hall and Flinker (1965) after Peterson and Chizzzo (1963) was used to elute the column. To produce the gradient a nine-chambered, continuous-flow device was used. The starting buffer was 0.01 M pH 8.0 and the limiting buffer 0.3 M pH 4.5. The volume of each chamber was 3 ml. The flow rate in different columns varied between 0.5–1.0 ml/hr without any effect on the separation. Fractions of 3 ml were collected and assayed for protein and radioactivity content. The fractions from these small columns were not used for further separation or characterization of the B₁₂ binders.

The so called "big column" technique of DEAE chromatography was used to process large amounts of labeled serum for further processing by other methods. DEAE-cellulose was packed to the height of 40 cm in a column with an internal diameter of 4 cm. The packing was performed in 4–5 steps, first by gravity and then by 10 pound air pressure. Up to 30 ml labeled serum was processed with these columns. The elution gradient was the same as described for "mini-columns". The volume of each chamber being 300 ml. The experiment was performed at a temperature of +4 °C with a flow rate of 30–40 ml/hr. Fractions of 30–40 ml were collected and aliquots taken for protein, radioactivity and B₁₂ assay. The fractions were pooled according to the radioactivity distribution, concentrated by ultrafiltration and dialyzed for subsequent procedures.

CM-cellulose chromatography

Carboxymethyl (CM) ion exchange cellulose (Whatman column media CM 11 made in England by W & R Bampton Ltd., nominal capacity 0.6 meq/g) was washed successively with ten volumes of 0.5 M HCl and 0.5 N NaOH. The acid and alkali were

washed off. It is then the washed cellulose is suspended in 0.03 M sodium chloride-sodium acetate buffer pH 5.4, and the pH of the mixture adjusted to 5.4. Thereafter the cellulose is rinsed several times with the box mentioned acetate buffer resuspended in it and stored at +4 C. It is used CM cellulose as employed.

A slurry of the cellulose in 0.03 M acetate buffer pH 5.4 is poured into column with an internal diameter of 1.5 cm and allowed to settle by gravity to the height of 45 cm. The sample which had been dialyzed against the same acetate buffer was layered on the column and eluted in. The first elution is performed with 0.03 M acetate buffer pH 5.4, followed by 0.057 M phosphate buffer pH 7.0, and completed with 0.5 M phosphate buffer pH 7.8. The outlet of the column was connected to a UV-absorber which indicated the elution of the protein fractions. The buffer was changed after the elution of protein peak.

The flow rate was kept at 60-80 ml/hr and fractions of 14 ml were collected and counted for radioactivity. The fractions are pooled according to the radioactivity peaks and concentrated for further use.

Gel filtration on Sephadex®

Sephadex G-200 made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia Fine Chemicals, Puerto Rico. The buffer used in the gel filtration experiments was 0.03 M phosphate buffer pH 7.4, made 0.8 M for NaCl and containing 0.05% sodium azide as preservative.

The gel was allowed to swell in the buffer for 72 hours prior to use. A slurry of it was poured to the height of 70 cm in silicone coated column with an internal diameter of 2.5 cm. The column was stabilized with the buffer for 4 hours. The same column was used repeatedly.

The dialyzed sample (phases 1-3 ml) was gently layered on the column, allowed to enter and washed in with three times 1 ml of the gel buffer. The column was eluted with the gel buffer at flow rate of 8-15 ml/hr. The outlet of the column was run through photorecorder recording the absorption at 260 mμ. Fractions of 8 ml were collected and counted for radioactivity. Either the UV recorder or chemical assay as employed to determine the protein concentration.

The molecular weight estimations from the gel filtration experiments were based on the linear correlation between the elution volume of molecule and the logarithm of its molecular weight (Andrew 1964). The amount of buffer needed to hit the peak

fraction was taken as the elution volume of the protein. The elution volume for the column was measured equally with Blue Dextran 2000 (Pharmacia) in order to eliminate the effect of possible alterations in the column during prolonged use. The ratio of elution volume to total volume was used instead of elution volume alone.

The following set of reference proteins (from Mann Research Laboratories Inc. New York, N.Y.) was used to produce the standard line illustrated in figure 1.

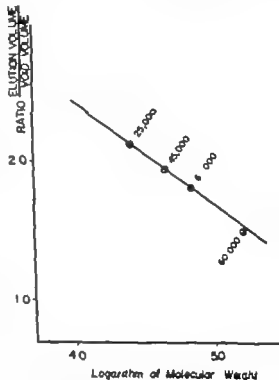


Fig 1 The standard line used for molecular weight estimations by Sephadex G-200 gel filtration.

- Chymotrypsinogen, molecular weight 25,000
 - Ovalbumin, molecular weight 43,000
 - Bovine albumin, molecular weight 67,000
 - Human gamma globulin, molecular weight 100,000
- This standard line was used to estimate molecular weight also for the filtrated samples.

Sephadex G-100 was treated similarly as G-200 and column with the dimensions of 2.4 x 85 cm was prepared. This column was used to fractionate 1-8 ml samples of rat liver serum. The protein distribution pattern recorded by the absorption at 260 mμ was used as reference to the location of the radioactivity peaks. No molecular weight estimations were performed on this column.

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B₁₂ binders

All the ⁵⁷CoB₁₂ labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioactive vitamin B₁₂ added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B₁₂ binding capacity of serum proteins (e.g. Miller 1948). The working solutions of ⁵⁷CoB₁₂ contained 300 pg in 0.14–0.21 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking. After incubating in a +37°C water bath for 30 minutes, the serum sample was dialyzed against the starting buffer of the next procedure, to remove any unbound B₁₂ and to equilibrate the sample. The serum sample was counted for radioactivity prior to and after the dialysis. Also the dialyzing fluid was counted and no radioactivity could be detected in it when the standard amount of ⁵⁷CoB₁₂ was added.

The labeled serum was then submitted for various procedures in order to fractionate the Hamin B₁₂ binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ion exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co., Acene, N.H. The capacity of the cellulose was 0.93 meq/g. The new cellulose powder as supplied in water stirred and allowed to sediment. The yellowish supernatant containing the finest particles was decanted off. This was repeated twice. The cellulose was then suspended in 0.5 N NaOH and stirred for 20–30 minutes. The alkali was washed off with water until the pH of the washing water reached 7.0. The same treatment was repeated with 0.5 N HCl and then again with 0.5 N NaOH. When the last alkali had been washed off the cellulose was suspended in 0.01 M phosphate buffer pH 8.0 and the pH of the mixture brought to 8.0 with 0.3 M NaH₂PO₄. The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphate buffer and suspended in it. The pH was again checked and readjusted, if necessary. Two-three drops of toluene per 1 liter of the mixture was added as a preservative. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A 50 capacity 3.9 meq/g, made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia Fine Chemicals, Piscataway, N.J. It was processed as also

using 0.5 N acid and alkali and suspended in 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Flakler (1963). Two modifications of the chromatography technique were used. The so called "mini-column technique" was used to study the B₁₂ binding pattern of small serum samples, in the range of 1 ml. Columns with an internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0.01 M phosphate buffer pH 8.0. The packing was performed in 3–4 steps, first by gravity and then by applying an air pressure of ten pounds on the column. The final length of the column was 3 cm. The labeled, dialyzed serum sample was layered on the column and washed in with the starting phosphate buffer. A concave phosphate buffer gradient of increasing molarity and decreased pH as modified by Hall and Flakler (1963) after Peterson and Chazotte (1962) was used to elute the column. To produce the gradient a nine-chambered, continuous-flow device was used. The starting buffer was 0.01 M pH 8.0 and the finishing buffer 0.3 M pH 4.5. The volume of each chamber was 23 ml. The flow rate in different columns varied between 5–7.0 ml/hr with no effect on the separation. Fractions of 3 ml were collected and assayed for protein and radioactivity content. The fractions from these small columns were not used for further separation or characterization of the B₁₂ binders.

The so called "big column technique" of DEAE-chromatography was used to process large amounts of labeled serum for further processing by other methods. DEAE-cellulose was packed to the height of 90 cm in a column with an internal diameter of 4 cm. The packing was performed in 4 steps, first by gravity and then by 10 pound air pressure. Up to 50 ml labeled serum was processed with these columns. The elution gradient was the same as described for "mini-column" the volume of each chamber being 300 ml. The experiment was performed at a temperature of +4°C with a flow rate of 30–40 ml/hr. Fractions of 30–40 ml were collected and aliquots taken for protein radioactivity and B₁₂ assay. The fractions were pooled according to the radioactivity distribution, concentrated by ultrafiltration and dialyzed for subsequent procedures.

CM-cellulose chromatography

Caboxymethyl (CM) ion exchange cellulose (Whatman column chromedia CM 11 made in England by W & H Balston Ltd., nominal capacity 0.6 meq/g) was washed successively with distilled water, 0.5 N HCl and 0.5 N NaOH. The bound alkali was

washed it with water the washed cellulose was suspended in 0.03 M sodium chloride-sodium acetate buffer pH 5.4, and the pH of the mixture adjusted to 5.4. Thereafter the cellulose as rinsed several times with the above mentioned acetate buffer resuspended in it and stored at +4 C. No need CM cellulose was employed.

A slurry of the cellulose in 0.03 M acetate buffer pH 5.4 as poured into column with an internal diameter of 1.5 cm and allowed to settle by gravity to the height of 45 cm. The sample which had been dialyzed against the same acetate buffer was layered on the column and washed in. The first elution as performed with 0.03 M acetate buffer pH 5.4, followed by 0.027 M phosphate buffer pH 7.0, and completed with 0.3 M phosphate buffer pH 7.8. The outlet of the column as connected to UV-recorder which indicated the elution of the protein fractions. The buffer as changed after the elution of protein peak.

The flow rate was kept at 60-65 ml/h and fractions of 14 ml are collected and counted for radioactivity. The fractions were pooled according to the radioactivity peaks and concentrated for further use.

Gel filtration on Sephadex®

Sephadex G-200 made by Pharmacia, Uppsala, Sweden, as purchased from Pharmacia Fine Chemicals, Parsippany NJ. The buffer used in the gel filtration experiments as 0.03 M phosphate buffer pH 7.4 made 0.5 M for NaCl and containing 0.02% sodium azide as preservative.

The gel as allowed to swell in the buffer for 72 hours prior to use. A slurry of it was poured to the height of 70 cm in silicone coated column with an internal diameter of 2.5 cm. The column was stabilized with the buffer for 24 hours. The same column was used repeatedly.

The dialyzed sample (eluate 1-2 ml) as gently layered on the column, allowed to enter and washed in with three times 1 ml of the gel buffer. The column was eluted like the gel buffer at flow rate of 6-15 ml/hr. The outlet of the column as run through photovolt recording the absorption at 290 mμ. Fractions of 2 ml are collected and counted for radioactivity. Either the UV-recorder or chemical assay as employed to determine the protein concentration.

The molecular weight estimations from the gel filtration experiments were based on the linear correlation between the elution volume of molecule and the logarithm of its molecular weight (Andrews 1964). The amount of buffer needed to elute the peak

fraction was taken as the elution volume of the protein. The old eluents for the column was measured equally with Blue Dextran 2000 (Pharmacia). In order to eliminate the effect of possible alterations in the column during prolonged use the ratio of elution volume of old eluent was used instead of elution volume alone.

The following set of reference proteins (from Mann Research Laboratories Inc., New York, N.Y.) was used to produce the standard line illustrated in figure 1.

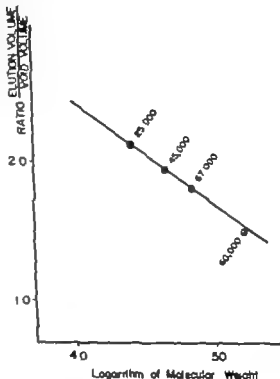


Fig. 1. The standard line used for molecular weight estimations by Sephadex G-200 gel filtration.

- Crystallin, molecular weight 23,000
 - Ovalbumin, molecular weight 45,000
 - Bovine albumin, molecular weight 67,000
 - Human gamma globulin, molecular weight 160,000
- This standard line as used to estimate molecular weight also for the filtrated samples.

Sephadex G-100 was treated similarly as *G-200* and column with the dimensions of 2.4 x 85 cm was prepared. This column was used to fractionate 1-2 ml samples of labeled serum. The protein distribution pattern recorded by the absorption at 290 mμ was used as reference to the location of the radioactivity peaks. No molecular weight estimations are performed on this column.

Electrophoresis

Geon block electrophoresis was performed using essentially the same methods as Hall and Finkler (1963). Geon number 497 polyvinylchloride resin was purchased from B. F. Goodrich Co., Niagara Falls, N.Y. The buffers used were 0.06 M barbiturate buffer pH 8.6 and 0.1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water stirred and filtered. The same treatment was repeated twice using the buffer. A wet semi-firm slurry was made with the buffer and poured into three, separated, parallel blocks of 45 cm x 8 cm x 1 cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with well soaked gauze bridges. The samples (CM purified binders or in some instances labeled serum) were dialyzed against the electrophoresis buffer and applied at the center of the block in a transverse slit of about 2-3 mm. The volume of the sample varied between 0.1-0.5 ml, depending on the level of concentration achieved by the preceding ultrafiltration and judged by the radioactivity of the sample. The starting voltage was 200 V (= 4.4 V/cm) and the running time 18-20 hours. The block was kept at a temperature of +4°C by a built-in cooling system in the electrophoretic apparatus. After the run the block was dried for 1-1.5 hours and then cut into 18 transverse segments of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distance from the point of application for the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used for further studies. The distribution of serum proteins recorded in a few experiments was measured by labeling the segments with 0.01 M phosphate buffer pH 8.0 and assaying the eluates for protein.

Uptake of ^3CoB by HeLa cells

The technique used was essentially the same as that described by Finkler and Hall (1967). HeLa cells in monolayer cultures were generously provided by Dr. J. V. Landau, Ph.D. the Biology Section of Veterans Administration Hospital, Albany, N.Y. The cell growth medium was decanted off and the dialyzed sample (CM purified binders in a volume of 1-3 ml) with Hank's base 199-IX (from Grand Island Biological Corporation, Grand Island, N.Y. catalog number 115 H) was added to the cells in a total volume of 15 ml. The cell bottles were then placed at +37°C for 2 hrs. After the incubation the medium was decanted off and the cell layers washed twice with buffered, ice cold solution containing 0.8 %

NaCl , 0.04 % KCl , 0.1 % dextrose and 0.033 % NaHCO_3 . The cells were then scraped from the bottle with a rubber tipped spatula and washed three times with centrifugation in the ice-cold buffered saline solution. The washed cells were suspended in 5 ml of the same solution. The amount of cells was counted in a hemocytometer using the standard laboratory technique for leukocyte counting. The cell suspension was counted for radioactivity.

Assay of vitamin B₁₂

The assays of vitamin B₁₂ were kindly performed by Mr. Edward B. Allen, using the *Escherichia gracilis* strain and the method described in detail by Hall and Allen (1964).

Concentration of the samples

The fractions or pooled fractions from the chromatographic procedures were concentrated for further use by ultrafiltrating them through Visking dialysis tubing (obtained from Union Carbide Corporation, Chicago, Ill.). The tubing was thoroughly washed, filled with the sample, and placed into reduced pressure in a vacuum flask at +4°C. The inside of the tubing was kept in open connection with the outside air. The reduced pressure was adjusted to a level which gave maximal expansion of the tubing without breaking it. Possible leaks were detected by counting the ultrafiltered outside fluid for radioactivity.

Dialysis

The dialysis of the samples against the appropriate buffer was performed in large Visking dialysis tubing. For DEAE-chromatography on "mini-column" a short dialysis of 1-2 hrs against 250 ml of the buffer was used. For other purposes the samples were dialyzed three successive times against 30-40 fold volumes and for 16-24 hours. Dialysis was performed at +4°C and a magnetic stirrer was used to mix the fluid.

Protein determination

The protein concentration in the chromatography fractions was measured by the method of Lowry *et al.* (1951). The protein distribution was used as a reference to the location of the radioactivity peaks. Hence only the optical densities from the photometer were recorded and the actual protein concentrations were not calculated.

All the reagents used in the present work were of Anala Grade quality.

Results

The binding of added B_{12} in normal adult serum

Twenty samples of normal adult serum were studied adding 300 pg of ^{57}Co -labeled B_{12} per 1 ml of serum and using the mini-column technique of DEAE-chromatography. The main binding of added B_{12} in the chromatograms was just before the main protein peak, i.e. in the TC II region (Hall and Finkler 1965). In addition to the main TC II-peak of radioactivity there was some binding of CoB_{12} to proteins eluted later from the column. The carrier of circulating native B_{12} , TC I is known to be eluted after the bulk of

protein (Hall and Finkler 1965) and a small amount of added B_{12} was found bound to it. A varying amount of added B_{12} was eluted in between these two regions. This amount was always a minor one and the complex was not characterized further. Figures 2 and 3 show the variation in the binding of small amounts of added B_{12} in the middle region of the chromatograms.

The binding of added B_{12} in cord serum

Ten different samples of cord serum were studied using the same technique as above. Three peaks of radioactivity could be consistently detected in the chromatograms. The first peak was located just prior to the main protein peak and thus corresponded to TC II

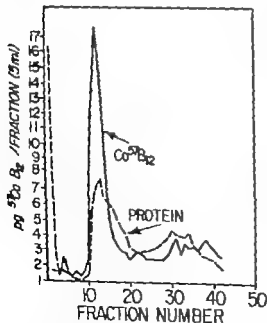


Fig. 2 DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg $^{57}\text{CoB}_{12}$. The peak of TC II is in fraction number 13, TC I is located in fractions 32-48.

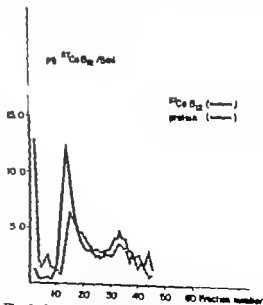


Fig. 3 DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg $^{57}\text{CoB}_{12}$.

Electrophoresis

Geon block electrophoresis was performed using essentially the same methods as Hall and Finkler (1962). Geon number 427 polyvinylchloride resin was purchased from B. I. Goodrich Co., Niagara Falls, N.Y. The buffers used were 0.05 M barbiturate buffer pH 8.0 and 0.1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water stirred and filtered. The same treatment was repeated twice using the buffer A wet, semi firm slurry was made with the buffer and poured into three separated, parallel blocks of 45 cm X 8 cm X 3 cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with well soaked gauze bridges. The samples (CM purified bladders or in some instances labeled serum) were dialyzed against the electrophoresis buffer and applied at the center of the block in a transverse slit of about -3 mm. The volume of the sample varied between 0.3-0.5 ml depending on the level of concentration achieved by the preceding ultrafiltration and judged by the radioactivity of the sample. The starting voltage was 200 V (=4.4 V/cm) and the running time 18-20 hours. The block was kept at a temperature of +4 C by a belt in cooling system in the electrophoretic apparatus. After the run the block was dried for 1-1.5 hours and then cut 1 to 10 transverse segments of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distances from the point of application for the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used for further studies. The distribution of serum proteins recorded in a few experiments was measured by eluting the segments with 0.01 M phosphate buffer pH 8.0 and assaying the eluates for protein.

Uptake of CoB_{12} by HeLa cells

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NaCl , 0.04 % HCl , 0.1 % dextrose and 0.033 % NaHCO_3 . The cells were then scraped from the bottle with a rubber-tipped spatula and washed three times with centrifugation in the ice-cold buffered saline solution. The washed cells were suspended in 5 ml of the same solution. The amount of cells was counted in a hemocytometer using the standard laboratory technique for leukocyte counting. The cell suspension was counted for radioactivity.

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Dialysis

The dialysis of the samples against the appropriate buffer was performed in bags of Visking dialysis tubing for D&B chromatography's "mini-columns". A short dialysis of 1-2 hours against 250 ml of the buffer was used for other purposes the samples were dialyzed three successive times against 30-40 fold volumes and for 16-24 hours. Dialysis was performed at +4 C and a magnetic stirrer was used to mix the fluid.

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The protein concentration in the chromatography fractions was measured by the method of Lowry et al. (1951). The protein distribution was used as a reference to the location of the radioactivity peaks. Hence, only the optical densities from the photometer were recorded, and the actual protein concentrations were not calculated.

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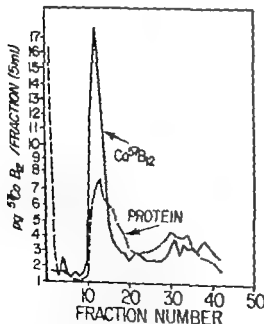


Fig. 1. DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg CoB_{12} . The peak of TC II is in fraction number 12, TC I is located in fractions 25–40.

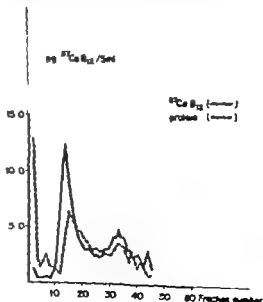


Fig. 2. DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg $^{57}\text{CoB}_{12}$.

Electrophoresis

Good block electrophoresis was performed using essentially the same methods as Hall and Flakler (1962). Good number 477 polyvinylchloride resin was purchased from H. P. Goodrich Co., Niagara Falls, N.Y. The buffers used were 0.06 M barbiturate buffer pH 8.6 and 0.1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water stirred and filtered. The same treatment was repeated twice using the buffer A wet semi firm slurry was made with the buffer and poured into three separated, parallel blocks of 48 cm × 8 cm × 3 cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with a well soaked gauze bridges. The samples (CM purified binders or in some instances labeled serum) were dialyzed against the electrophoretic buffer and applied at the center of the block in a transverse slit of about 2–3 mm. The volume of the sample varied between 0.2–0.5 ml, depending on the level of concentration achieved by the preceding ultrafiltration and judged by the radioactivity of the sample. The starting voltage was 200 V (=4.4 V/cm) and the running time 18–20 hours. The block was kept at a temperature of +4°C by a built in cooling system in the electrophoretic apparatus. After the run the block was dried for 1–1.5 hours and then cut into 16 transverse segments of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distance from the point of application to the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used for further studies. The distribution of serum proteins recorded in a few experiments was measured by eluting the segments with 0.01 M phosphate buffer pH 8.0 and assaying the eluates for protein.

Uptake of CoB by HeLa cells

The technique used was essentially the same as that described by Flakler and Hall (1967). HeLa cells in monolayer cultures were generously provided by Dr. J. V. Lasdan, Ph.D. the Biology Section of Veterans Administration Hospital, Albany, N.Y. The cell growth medium was decanted off and the dialyzed sample (CM purified binders in a volume of 1–2 ml) with Hask's base 199-IX (from Grand Island Biological Corporation, Grand Island, N.Y. catalog number 115 II) was added to the cells in a total volume of 12 ml. The cell bottles were then placed at +37°C for 3 hrs. After the incubation the medium was decanted off and the cell layers washed twice with buffered, ice-cold solution containing 0.8 %

NaCl, 0.04 % KCl, 0.1 % dextrose and 0.01 % NaHCO₃. The cells were then scraped from the bottle with a rubber-tipped spatula and washed three times with centrifugation in the ice-cold buffered saline solution. The washed cells were suspended in 5 ml of the same solution. The amount of cells was counted in a hemocytometer using the standard laboratory technique for leukocyte counting. The cell suspension was counted for radioactivity.

Assay of vitamin B₁₂

The assays of vitamin B₁₂ were kindly performed by Mr. Edward S. Allen, using the *Escherichia gracilis* strain and the method described in detail by Hall and Allen (1964).

Concentration of the samples

The fractions or pooled fractions from the chromatographic procedures were concentrated for further work by ultrafiltrating them through Visking dialysis tubing (obtained from Union Carbide Corporation, Chicago, Ill.) The tubing was thoroughly washed, filled with the sample and placed into reduced pressure in a vacuum flask at +4°C. The inside of the tubing was kept in open connection with the outside air. The reduced pressure was adjusted to a level which gave maximal expansion of the tubing without breaking it. Possible leaks were detected by counting the ultrafiltered outside fluid for radioactivity.

Dialysis

The dialysis of the samples against the appropriate buffer was performed in bags of Visking dialysis tubing for DEAE chromatography on mini-columns. A short dialysis of 1–2 hrs against 250 ml of the buffer was used. For other purposes the samples were dialyzed three successive times against 30–40 fold volumes and for 10–14 hours. Dialysis was performed at +4°C and a magnetic stirrer was used to mix the fluid.

Protein determination

The protein concentration in the chromatography fractions was measured by the method of Lowry et al. (1951). The protein distribution was used as a reference to the location of the radioactivity peaks. Hence, only the optical densities from the photometer were recorded and the total protein concentrations were not calculated.

All the reagents used in this present work were of Analaar Grade quality.

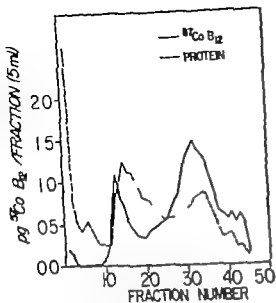


Fig 7. DEAE-cellulose chromatogram of 1 ml of cord serum with 50 pg $^{57}\text{CoB}_{12}$.

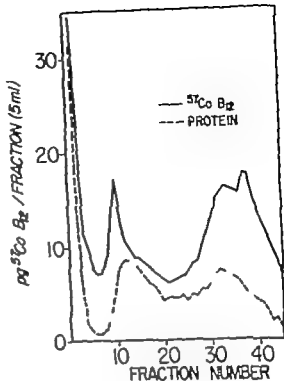


Fig 8. DEAE-cellulose chromatogram of 1 ml of cord serum with 1000 pg $^{57}\text{CoB}_{12}$. 72 % of the added labeled vitamin B₁₂ was bound.

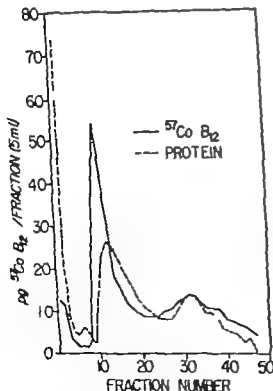


Fig 9. DEAE-cellulose chromatogram of 1 ml of cord serum with 1000 pg $^{57}\text{CoB}_{12}$. 88 % of the added labeled vitamin B₁₂ was bound.

from the 1000 pg/ml experiments. The amounts of added B₁₂ bound in these experiments were 88 % and % respectively

The binding of added B₁₂ in infant serum

Twenty five serum samples from infants ranging in age from 1 to 158 days were studied using the "mini-column technique" of DEAE-chromatography. Although the level of separation did not permit quantitated comparisons between the different chromatograms, the binding to FTC was easily detected and roughly graded as strong, moderate, or slight as compared to the binding to TC II. Table 1 presents the list of these chromatograms. The youngest infant whose serum did not give the cord serum pattern was 10 days old. On the other hand, a sample taken from a 106 days old infant still con-

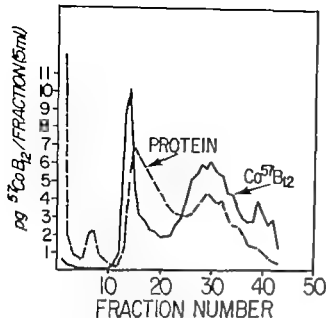


Fig 4. DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg CoB_{12} . The peak fractions for TO II FTC and TO I are 14, 30 and 39 respectively.

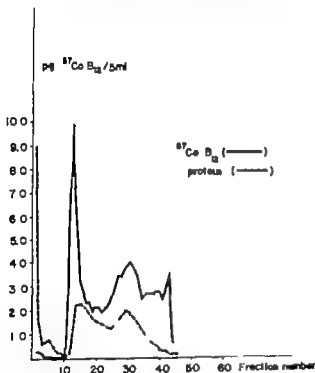


Fig 5. DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg $^{57}\text{CoB}_{12}$.

The third peak, which contained the least amount of $^{57}\text{CoB}_{12}$, was at the end of the chromatogram in the TO I region. The second peak in between these two was located corresponding to the minor uncharacterized binder

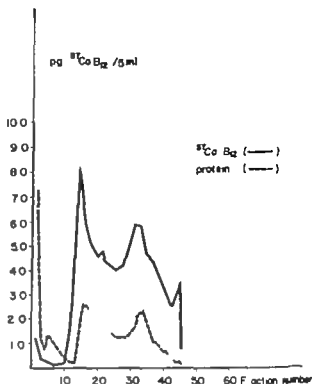


Fig 6. DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg $^{57}\text{CoB}_{12}$.

in adult chromatograms. It occurred in all the samples studied. Figure 4 shows a typical chromatogram of cord serum with 300 pg of labeled B₁₂ added per 1 ml. Figures 5 and 6 show the variation in the amounts of added B₁₂ bound to TO II and to the middle binder which will be referred to as the fetal transcobalamin FTC.

Five samples of cord serum were studied adding small amounts of labeled B₁₂ to the serum. One sample was studied with an addition of 30 pg/ml two with 50 pg/ml and two with 100 pg/ml. In all of these a definite peak of radioactivity was found in the FTC region. Figure 7 shows a chromatogram of cord serum with 50 pg of labeled B₁₂ per 1 ml.

To four cord serum samples 1000 pg of labeled B₁₂ was added per 1 ml and the samples were submitted to chromatography as above. Under these conditions the added B₁₂ was not completely bound and the percentages of binding were 54, 63, 72 and 88%. Figures 8 and 9 show two types of chromatograms.

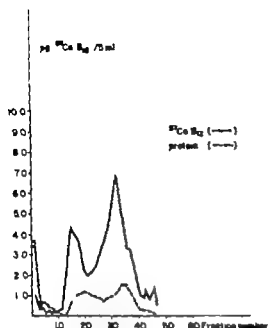


Fig. 10 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Age one day. Experiment number 2 in table 1.

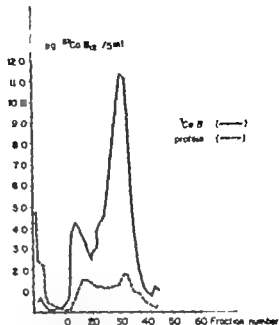


Fig. 12 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby M, age three days. Experiment number 3 in table 1.

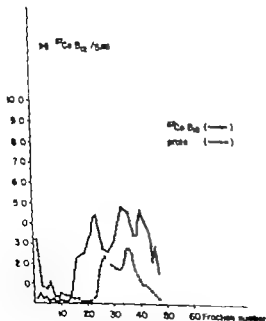


Fig. 11 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby R, age three days. Experiment number 4 in table 1.

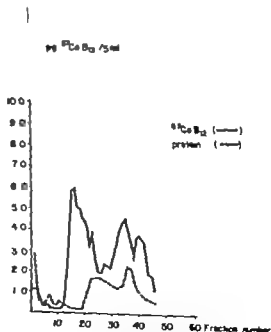


Fig. 13 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby R, age eight days. Experiment number 6 in table 1.

Table 1 *DEAE-chromatograms of infant serum samples*

Experiment number	Age (days)	Binding of added B_{12} to FTC	Figure	Binding of added B_{12} to the FTC-like binder in the mother
1	1	strong		strong
	1	strong	10	strong
3	3	strong		strong
4	3	strong	11	intermediate
5	3	strong	12	intermediate
6	8	moderate	13	intermediate
7	10	slight	14	absent
8	10	moderate		absent
9	11	strong		intermediate
10	11	strong		strong
11	17	moderate	15	intermediate
12	30	moderate		strong
13	30	moderate	16	intermediate
14	35	strong		
15	41	slight		
16	46	moderate		
17	53	slight		
18	54	strong		
19	60	slight		
20	77	strong		
21	80	strong		
22	86	slight	17	
23	90	slight		
4	106	moderate	18	
25	158	slight		

tained a definite binder with the chromatographic properties of FTC. Illustrative examples of the different infant serum chromatograms can be seen in figures 10 through 18.

Some of the 25 samples were drawn from

the same infants at different ages. Table 2 gives a summary of these chromatograms. Figures 11, 13 and 16 and figures 12 and 15 illustrate the changing pattern of B_{12} binding in these serial samples.

Table 2. *DEAE-chromatograms of serial infant samples*

Name	Experiment number (table 1)	Age (days)	Binding to FTC	Figure
Baby V	1	1	strong	
	3	3	strong	
	13	30	moderate	
Baby R.	4	3	strong	11
	6	8	moderate	13
	13	30	moderate	16
Baby M.	5	3	strong	15
	9	11	strong	
	11	17	moderate	15

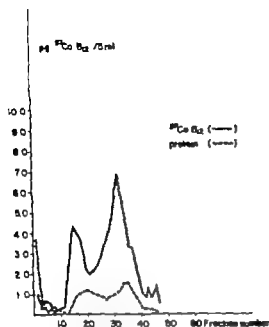


Fig 10. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Age one day. Experiment number 2 in table 1.

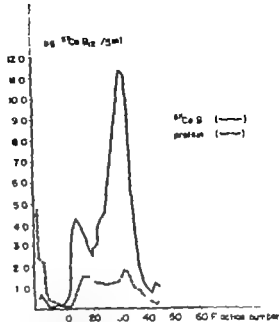


Fig 11. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby M, age three days. Experiment number 5 in table 1.

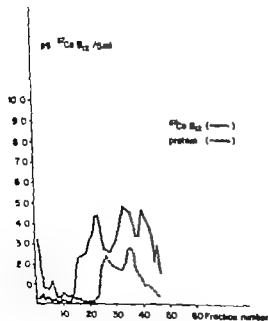


Fig 11. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby M, age three days. Experiment number 4 in table 1.

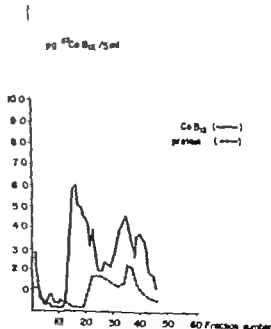


Fig 12. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby R, age eight days. Experiment number 6 in table 1.

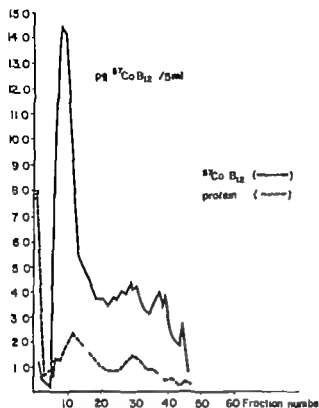


Fig. 14. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Age ten days. Experiment number 7 in table 1

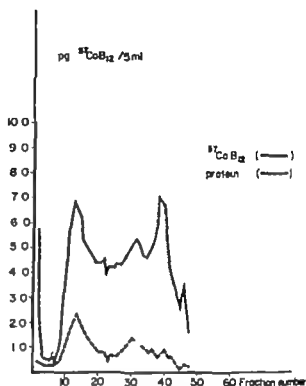


Fig. 16. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby R, age 28 days. Experiment number 13 in table 1

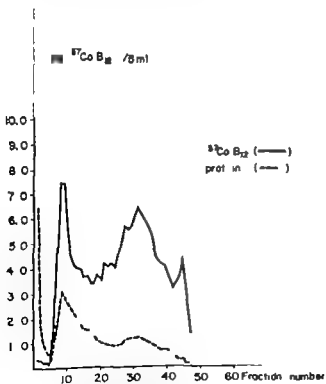


Fig. 15. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Baby M, age 17 days. Experiment number 11 in table 1

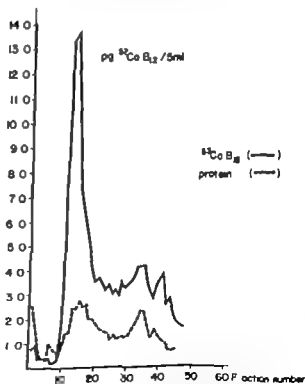


Fig. 17. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{CoB}_{12}$. Age 86 days. Experiment number 23 in table 1

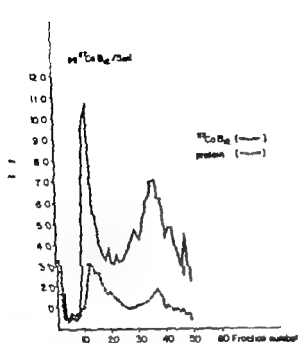


Fig. 18. DEAE-cellulose chromatogram of 1 ml of infant serum with 500 pg $^{51}\text{CrCoB}_{12}$. Age 109 days. Experiment number 24 in table 1.

The binding of added B_{12} in maternal serum

Sera from twelve delivering or newly delivered mothers were studied by DEAE-chromatography. Three of the samples gave the classical adult binding pattern with almost all of the added B_{12} bound to TC II. In five samples a small peak of radioactivity was found corresponding to the location of FTC. However this peak was not larger than that found in some of the normal adult samples. In the remaining four samples a considerable amount of the added B_{12} was bound to the FTC-like binder and the chromatograms of these cases were indistinguishable from the cord serum chromatograms. Figures 19, 20 and 21 illustrate the three different types of maternal chromatograms. All three types of chromatograms were obtained both in the pre-delivery and in the post delivery group of samples. The type of the maternal B_{12} binding pattern for the studied paired mother-child samples is given in Table 1.

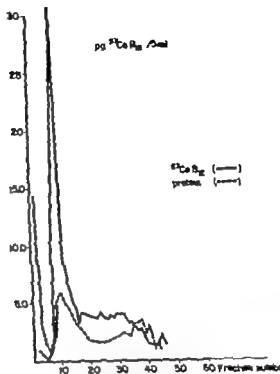


Fig. 19. DEAE-cellulose chromatogram of 1 ml of serum from delivering mother with 500 pg $^{51}\text{CrCoB}_{12}$. Experiment number 8 in table 1 is of the child of the mother.

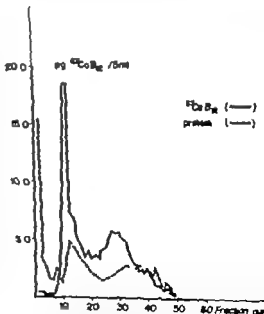


Fig. 20. DEAE-cellulose chromatogram of 1 ml of serum from delivering mother with 500 pg $^{51}\text{CrCoB}_{12}$. Experiments number 4, 6 and 12 in table 1 and 4.

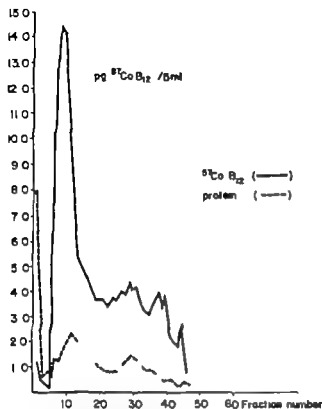


Fig 14. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{Co B}_{12}$. Age ten days. Experiment number 7 in table 1

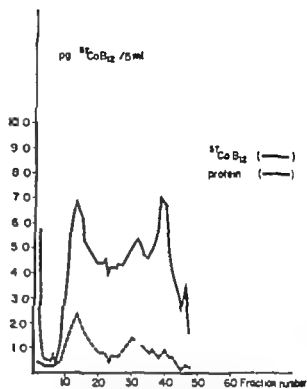


Fig 16. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{Co B}_{12}$. Baby R, age 30 days. Experiment number 13 in table 1

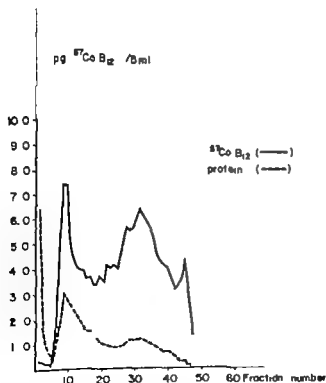


Fig 15. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{Co B}_{12}$. Baby M., age 17 days. Experiment number 11 in table 1

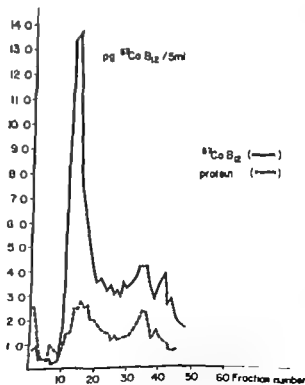


Fig 17. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}\text{Co B}_{12}$. Age 86 days. Experiment number 23 in table 1

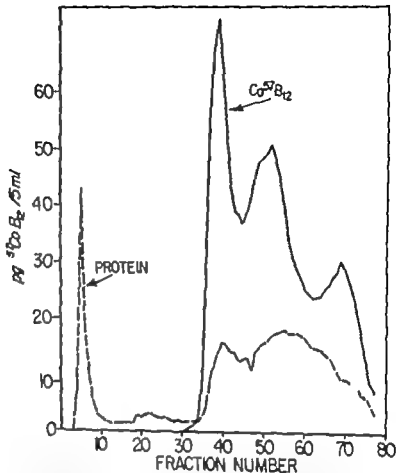


Fig. 23. DHAF column chromatogram of 50 ml of cord serum with 300 $\mu\text{g/ml}$ $^{125}\text{I-CoB}_{12}$. The peak fractions for $^{125}\text{I-CoB}_{12}$ and protein are 40 and 7, respectively.

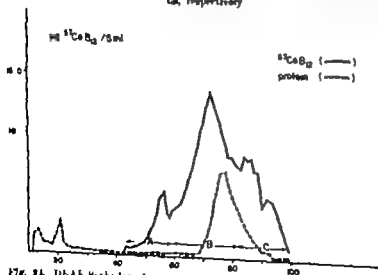


Fig. 24. DHAF Sephadex chromatogram of 10 ml of cord serum with 300 $\mu\text{g/ml}$ $^{125}\text{I-CoB}_{12}$. The dimensions of the column were 8×11 cm.

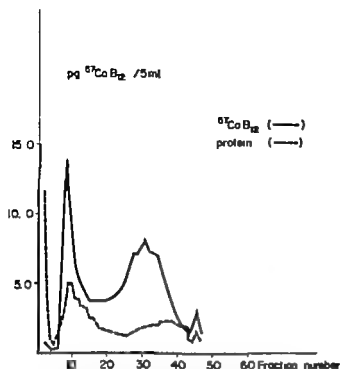


Fig. 1 DEAE-cellulose chromatogram of 1 ml of serum from a delivering mother with 300 µg CoB_{12} . Experiment number 10 in table 1 is of the child of this mother

Characterization of the B_{12} binders in cord serum

DEAE-chromatography on big columns

DEAE-chromatography on a big column was used as a starting procedure in the characterization of the individual binders. Figure 22 shows a chromatogram of 40 ml of normal adult serum with 125 µg of $^{67}\text{CoB}_{12}$ added per 1 ml. Eight lots of cord serum were processed in the same manner and the resulting chromatograms showed three activity peaks analogous to those described previously. Figure 23 shows a chromatogram of 50 ml of cord serum with 300 µg of labeled B_{12} added per 1 ml.

One lot of cord serum was processed using DEAE-Sephadex® instead of DEAE-cellulose. This chromatogram illustrated in figure 24, had a slightly different appearance but still contained the same components.

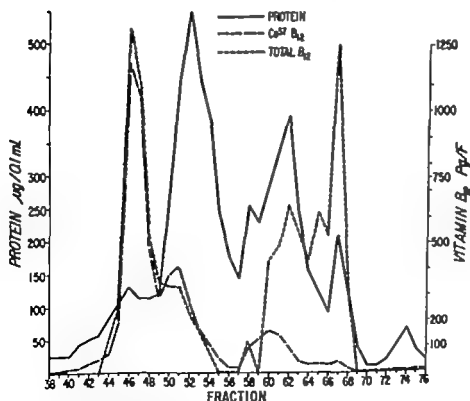


Fig. 22 DEAE-cellulose chromatogram of 40 ml of normal adult serum with 125 µg/ml $^{67}\text{CoB}_{12}$. Total B_{12} is the result of the *E. glauca gracilis* assay. Fractions 1-37 did not contain radioactivity and were not illustrated. The peak of TC II is in fraction 46, that of TC I in fraction 67.

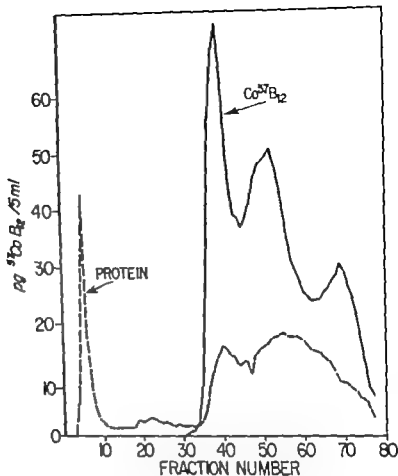


Fig. 13. DEAE-cellulose chromatogram of 50 ml of cord serum with 300 pg/ml $^{57}\text{CoB}_{12}$. The peak fractions for TO II, FTC and TO I are 40, 53 and 60 respectively

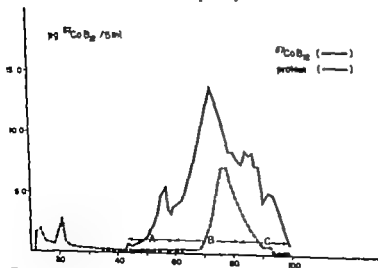


Fig. 14. DEAE Sephadex chromatogram of 10 ml of cord serum with 300 pg/ml $^{57}\text{CoB}_{12}$. The dimensions of the column were 3×11 cm.

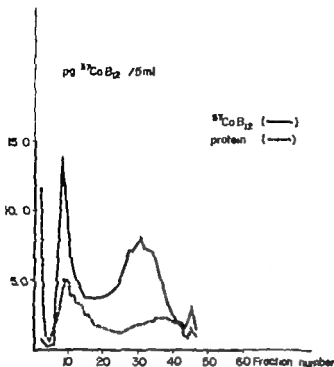


Fig 1. DEAE-cellulose chromatogram of 1 ml of serum from a delivering mother with 300 pg $^{57}\text{CoB}_{12}$. Experiment number 10 in table 1 is of the child of this mother

Characterization of the B₁₂ binders in cord serum

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DEAE-chromatography on a big column was used as a starting procedure in the characterization of the individual binders. Figure 23 shows a chromatogram of 40 ml of normal adult serum with 125 pg of $^{57}\text{CoB}_{12}$ added per 1 ml. Eight lots of cord serum were processed in the same manner and the resulting chromatograms showed three activity peaks analogous to those described previously. Figure 23 shows a chromatogram of 50 ml of cord serum with 300 pg of labeled B_{12} added per 1 ml.

One lot of cord serum was processed using DEAE-Sephadex® instead of DEAE-cellulose. This chromatogram illustrated in figure 4 had a slightly different appearance, but still contained the same components.

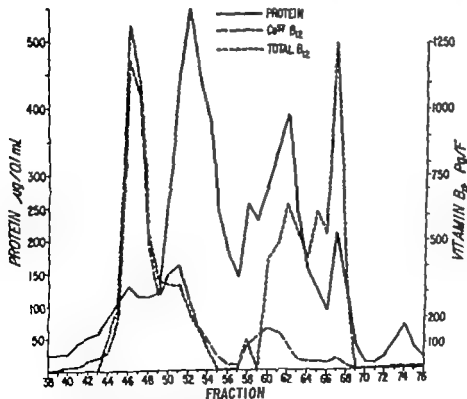


Fig 22. DEAE-cellulose chromatogram of 40 ml of normal adult serum with 125 pg/ml $^{57}\text{CoB}_{12}$. Total B_{12} is the result of the *E. gossii gracilis* assay. Fractions 1—37 did not contain radioactivity and were not illustrated. The peak of TC II is in fraction 46, that of TC I in fraction 62.

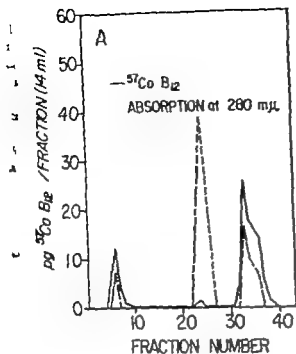


Fig. 26. CM-cellulose chromatogram of the A-peak from the DEAE-cellulose chromatography illustrated in figure 25.

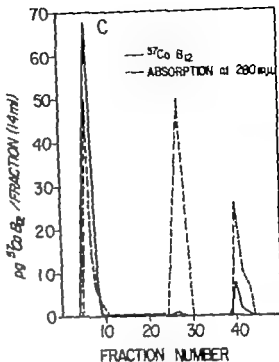


Fig. 28. CM-cellulose chromatogram of the C-peak from the DEAE-cellulose chromatography illustrated in figure 27.

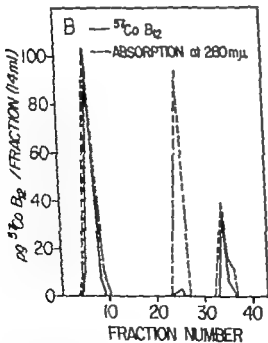


Fig. 27. CM-cellulose chromatogram of the B-peak from the DEAE-cellulose chromatography illustrated in figure 23.

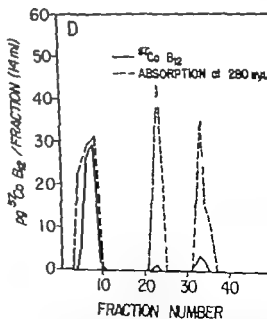


Fig. 29. CM-cellulose chromatogram of the D-peak from the DEAE-cellulose chromatography illustrated in figure 29.

CM-cellulose chromatography

The activity peaks from DEAE-chromatographies were ultrafiltered and dialyzed for chromatography on carboxymethyl cellulose columns. Figures 25 through 29 illustrate a DEAE-chromatogram with the subsequent CM-cellulose chromatograms of its different activity peaks.

The first DEAE-peak (A) consisted mainly of material eluted from the CM-column by the final buffer. This material was called CM purified TC II and was used for the further characterization of the properties of TC II.

The second DEAE-peak (B) was mainly eluted from the CM-cellulose by the starting buffer. This non retaining material was called CM purified FTC. The retaining part of the B-peak, or that which was later eluted with the final buffer can be considered to result from the contamination with the A peak.

The third DEAE-peak as well as the last part of the chromatogram (C and D) still contained trace amounts of TC II like material. The main part of these peaks was non

retaining i.e. eluted with the starting buffer and referred to as CM purified TC I.

The CM-chromatography did not separate FTC and TC I but it did separate them from TC II and eliminate a large amount of the non B binding proteins.

When the radioactivity peaks from the DEAE-Sephadex run (figure 24) were processed by CM-chromatography 55%, 22% and 48% of the A, B- and C-peaks, respectively were found to have the properties of TC II in CM-chromatography that is they were retained until the final buffer. This spreading of TC II could already be seen in the low appearance of the A peak in the DEAE-Sephadex chromatogram.

Electrophoretic studies

The CM purified binders from five different DEAE-chromatographies were concentrated by ultrafiltration and dialyzed against the appropriate buffer prior to electrophoresis. Because of the differences in the properties of the gel and the possible differences in the electric current between the individual ex-

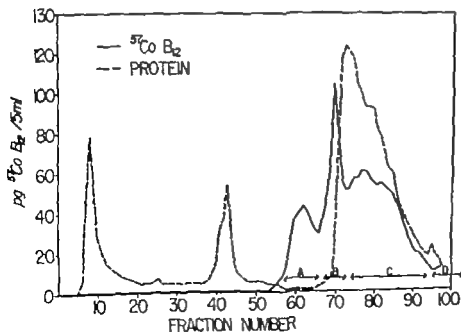


Fig. 25. DEAE-cellulose chromatogram of 50 ml of cord serum with 300

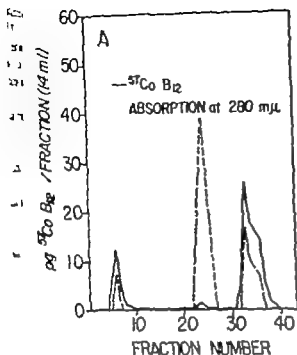


Fig. 24. CM-cellulose chromatogram of the A peak from the DEAE-cellulose chromatography illustrated in figure 23.

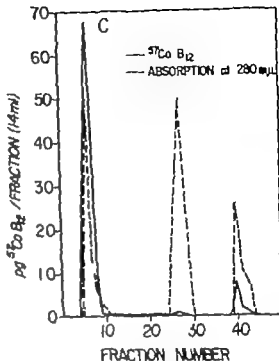


Fig. 25. CM-cellulose chromatogram of the C peak from the DEAE-cellulose chromatography illustrated in figure 23.

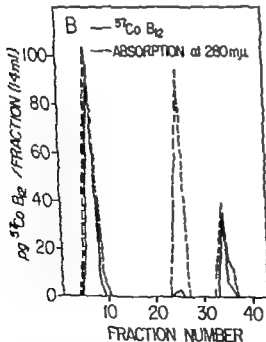


Fig. 27. CM-cellulose chromatogram of the B peak from the DEAE-cellulose chromatography illustrated in figure 23.

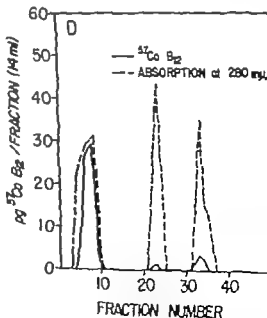


Fig. 28. CM-cellulose chromatogram of the D peak from the DEAE-cellulose chromatography illustrated in figure 23.

periments, the measured mobility of the same protein is not necessarily the same for each experiment. Thus no direct comparisons can be made between different experiments, only the mobilities of proteins run in parallel on the same block can be compared.

Electrophoresis at pH 8.6 Eleven experiments with two or three parallel samples were

Table 3. *Electrophoresis at pH 8.6*

Nro	Blinder	Mobility (cm)
1	FTC	+3
	TC II cord serum	+1
	TC II, adult serum	+1
2	TC II adult serum	+1
	FTC	+1
	TC I cord serum	+3
3	TC II adult serum	+4
	FTC	+4
	TC I cord serum	+7
4	TC II, adult serum	+4
	FTC	+5
5	TC II, adult serum	+3
	FTC	+4
	TC I, cord serum	+6
6	TC II, cord serum	+3
	FTC	+6
	TC I, cord serum	+8
7	TC II cord serum	+4
	FTC	+6
	TC I cord serum	+9
8	TC II, cord serum	+3
	FTC	+4
	TC I, cord serum	+3
9	TC II, adult serum	+
	FTC	+3
	TC I, cord serum	+5
10	TC II adult serum	+3
	FTC	+4
	TC II cord serum	+3
11	TC II adult serum	+3
	TC II, cord serum	+3
	TC I, cord serum	+6

performed. Table 3 gives the mobilities for the different binders in these experiments. The mobility of TC II from cord serum was the same as the mobility of TC II from adult serum. FTC had a mobility between TC I and TC II. Figures 30 through 33 are selected to illustrate the electrophoretic behavior of the $^{57}\text{CoB}_{12}$ -protein complexes. Figure 30 also includes the distribution of serum proteins in the gel block. TC I moved in the fast α -globulin region and TC II in the β -globulin region. FTC which had an intermediate mobility was thus found in the α -globulin region.

Electrophoresis at pH 4.5 Four electrophoretic experiments with three $^{57}\text{CoB}_{12}$ protein complexes in each were performed at pH 4.5. Table 4 gives the mobilities observed in these experiments. Figures 34 and 35

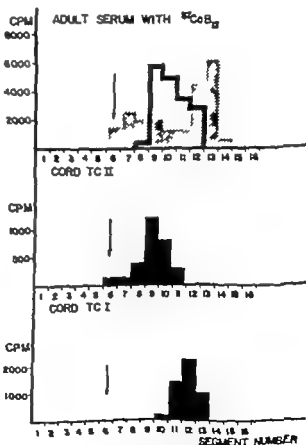


Fig 30. Geon block electrophoresis at pH 5.5. The black columns represent radioactivity in the segments. The shaded columns represent the amount of protein eluted from the segments. The arrow points to the segment of application.

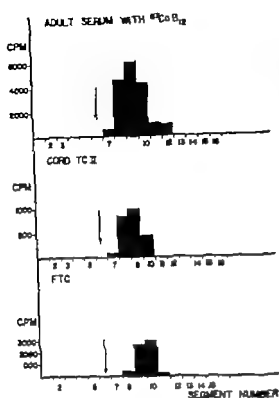


Fig. 21. Gamma block electrophoresis at pH 8.6.

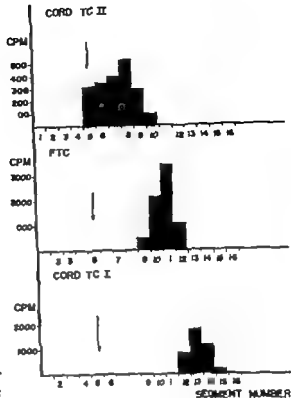


Fig. 22. Gamma block electrophoresis at pH 8.6.

illustrate two of the experiments. TC II stayed at the point of application or had a slightly cathodal mobility and TC I had an anodal mobility. FTC had an anodal mobility which was somewhat less than that of TC I.

Table 4. Electrophoresis at pH 4.5

N	Bladder	Mobility (cm)
12	FTC	+2
	TO II, cord serum	0
	TO II, adult serum	II
13	TO II, adult serum	-1
	FTC	+2
	TO I, cord serum	+3
14	TO II, cord serum	II
	FTC	+3
	TO I, cord serum	+3
15	TO II, cord serum	0
	FTC	+2
	TO I, cord serum	+4

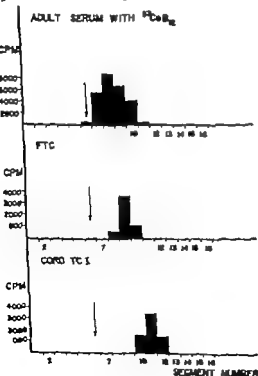


Fig. 23. Gamma block electrophoresis at pH 4.5.

periments, the measured mobility of the same protein is not necessarily the same for each experiment. Thus no direct comparisons can be made between different experiments, only the mobilities of proteins run in parallel on the same block can be compared.

Electrophoresis at pH 8.6 Eleven experiments with two or three parallel samples were

Table 3 *Electrophoresis at pH 8.6*

N ₁₀	Binder	Mobility (cm)
1	FTC	+3
	TC II, cord serum	+1
	TC II, adult serum	+1
2	TC II, adult serum	+1
	FTC	+1
	TC I, cord serum	+3
3	TC II, adult serum	+4
	FTC	+4
	TC I, cord serum	+7
4	TC II, adult serum	+4
	FTC	+5
5	TC II, adult serum	+3
	FTC	+4
	TC I, cord serum	+6
6	TC II, cord serum	+3
	FTC	+6
	TC I, cord serum	+8
7	TC II, cord serum	+4
	FTC	+6
	TC I, cord serum	+9
8	TC II, cord serum	+3
	FTC	+4
	TC I, cord serum	+5
9	TC II, adult serum	+2
	FTC	+3
	TC I, cord serum	+5
10	TC II, adult serum	+3
	FTC	+4
	TC II, cord serum	+3
11	TC II, adult serum	+3
	TC II, cord serum	+3
	TC I, cord serum	+6

performed. Table 3 gives the mobilities for the different binders in these experiments. The mobility of TC II from cord serum was the same as the mobility of TC II from adult serum. FTC had a mobility between TC I and TC II. Figures 30 through 33 are selected to illustrate the electrophoretic behavior of the $^{57}\text{CoB}_{12}$ -protein complexes. Figure 30 also includes the distribution of serum proteins in the geon block. TC I moved in the fast α -globulin region and TC II in the β -globulin region. FTC which had an intermediate mobility was thus found in the α_2 -globulin region.

Electrophoresis at pH 4.5 Four electrophoretic experiments with three CoB_{12} protein complexes in each were performed at pH 4.5. Table 4 gives the mobilities observed in these experiments. Figures 34 and 35

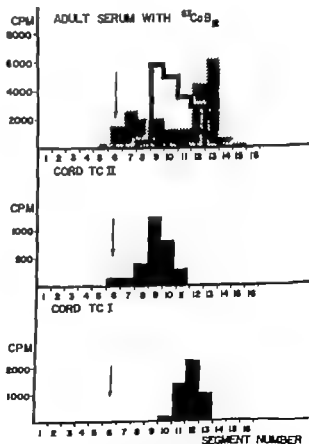


Fig. 30 Geon block electrophoresis at pH 8.6. The black columns represent radioactivity in the segments. The shaded columns represent the amount of protein eluted from the segments. The arrow points to the segment of application.

column was used to study the behavior of labeled whole serum on gel filtration.

Gel filtration of purified binders. CM purified binders from five different DEAE-chromatographies were studied. Table 5 summarizes the results. The molecular size of FTC was found to correspond to a molecular weight of 123,000. The molecular size of TC I did not differ from that of PTY.

Gel filtration of CoB labeled serum. Twelve experiments were performed using cord serum samples labeled with $^{57}\text{CoB}_{12}$. Seven different sera were studied and five of these with two amounts of labeled B_{12} added to them, 300 pg/ml and 3000 pg/ml. Two sera were studied only with 300 pg/ml. The experiments are listed in Table 6. The B binders were separated into two peaks. One was eluted before the albumin peak and thus consisted of material which had a molecular size larger than albumin. As shown above both FTC and TC I are included in this group. The other peak appeared after albumin as described for TC II by Ham *et al* (1966).

Therefore the large binders (FTC and TC I) made up one peak and TC II the other as eluted from Sephadex G 100 columns. The average amount of added B bound to the large binders was 52.6 % with a range from 4 % to 89 %. The amount of added B had little influence on its distribution between the binders. No systematic study was performed on the distribution of added B_{12} in normal adult serum. Only three experiments were performed on adult material with 300 pg of ^{57}CoB added per 1 ml. 16 %, 10 % and 15 % of the added B_{12} was bound to the large binders. Figure 36 illustrates one of the adult experiments and figure 37 the experiment number 3 on cord serum (300 pg/ml added).

The content of native B in the different binders

When the fractions from a DEAE-chromatogram of normal adult serum were assayed for their content of vitamin B₁₂, figure 22 resulted. Figure 38 is a differentially constructed illustration of the same run

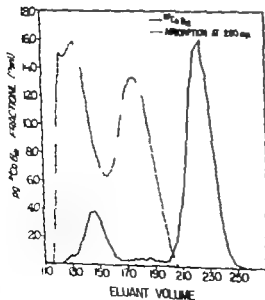


Fig. 36 Sephadex G-100 gel filtration of 1 ml of normal adult serum with 300 pg $^{57}\text{CoB}_{12}$. Eluent eluate is represented in ml.

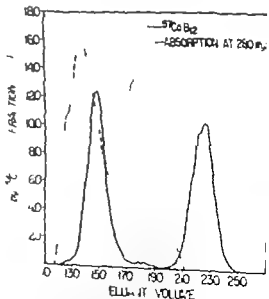


Fig. 37 Sephadex G-100 gel filtration of 1 ml of cord serum with 300 pg $^{57}\text{CoB}_{12}$. Eluent eluate is represented in ml.

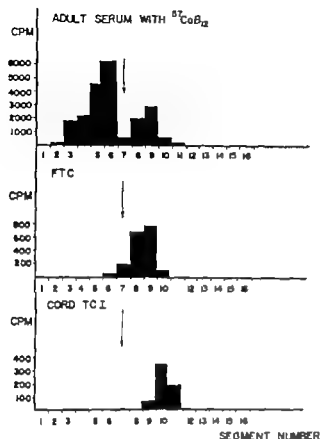


Fig. 34. Gel block electrophoresis at pH 4.5.

Gel filtration on Sephadex® columns

Gel filtration on Sephadex was used for two purposes. Sephadex G 200 column was used to estimate the molecular sizes of the CM purified B binders, and Sephadex G 100

Table 5. Molecular weight estimations by Sephadex G 200 gel filtration

FTC	TC I
153,000	143,000
110,000	92,000
103,000	103,000
135,000	140,000
145,000	115,000
92,000	140,000
100,000	
120,000	Range 92,000—145,000
	Mean 100,000

Range: 92,000—145,000
Mean 123,000

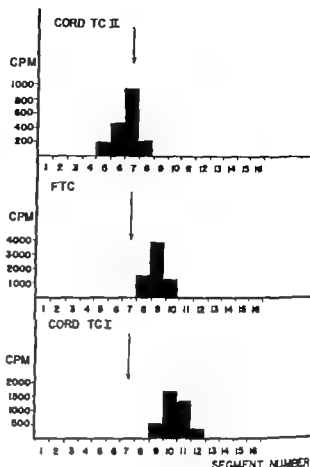


Fig. 33. Gel block electrophoresis at pH 4.5.

Table 6. Sephadex G 100 gel filtration of CoB labeled cord serum

	% B_{12} added pg/ml	% of radio- activity in TC II	% of radio- activity in large binders
1	300	50	50
	300	45	55
	2000	30	40
3	300	48	5
	2000	48	48
4	100	70	4
	2000	8	22
5	100	6	28
	2000	6	4
6	300	70	11
	2000	43	5
7	300	11	59

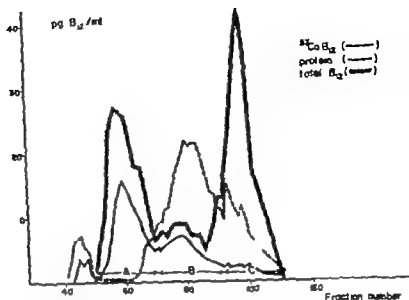


Fig. 40. DEAE-cellulose chromatogram of 20 ml of cord serum with 200 pg/ml $^{57}\text{CoB}_{12}$. Fractions 1–40 did not contain radioactivity and were omitted from the illustration.

10 pg, total B_{12} and $^{57}\text{CoB}_{12}$, respectively. These figures are influenced by the incomplete separation on the DEAE-column.

The second DEAE-column was run using 116 ml of cord serum where 10 pg $^{57}\text{CoB}_{12}$ /ml was added. Here the first radioactivity peak contained 2310 pg of B_{12} , the second 1950 pg, and the third 2410 pg as assayed by *Euglena*. The high amount of B_{12} in the second peak (FTC) was not in agreement with the results from the column described above. Furthermore, the sum of the B values was 6705 pg, which makes the B_{12} concentration in the original sample 568 pg/ml. The serum was assayed in the same run and its B_{12} concentration was found to be 406 pg/ml. The B_{12} in the FTC-peak was mainly found in two fractions which gave high readings. These fractions were preceded, followed, and separated from each other by fractions containing little B_{12} . Thus, there is evidence that in this run the B_{12} content in FTC was an artefact, probably due to contamination.

The third DEAE-chromatography used 30 ml of cord serum with 300 pg radioactive B_{12}

added per 1 ml. Figure 40 illustrates the results of this run. When the difference between total and added B_{12} for each peak was calculated, the A-peak (TC II) was found to contain 4295 pg of native B_{12} , the B-peak (FTC) 1211 pg, and the C-peak (TC I) 9581 pg. As can be seen from figure 40, part of the native B_{12} in the B-region was due to TC I.

Thus, these three DEAE-chromatograms show the presence of native B_{12} in the TC II fraction of cord serum besides the main location of it in TC I. They also indicate the absence of significant amounts of native B_{12} in FTC.

The uptake of vitamin B by HeLa cells from different $^{57}\text{CoB}_{12}$ -protein complexes

CM purified binders from five different cord serum DEAE-chromatographies were used. The data from the cell uptake experiments is presented in detail in Table 7. The same data grouped for each binder is presented in Table

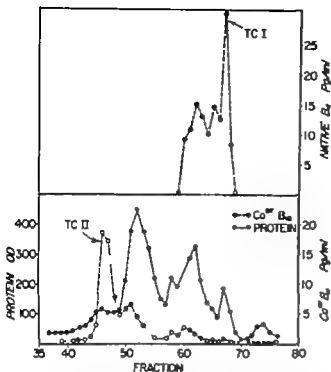


Fig 38. A reconstruction of figure 22 to demonstrate the differences in the location between native B_{12} and *in vitro* added $^{57}\text{Co}B_{12}$ in a DEAE-cellulose chromatogram of normal adult serum.

where 125 pg/ml labeled B_{12} was added to 40 ml of normal adult serum and the chromatography performed on a big DEAE

column. Total B_{12} was measured by the *Euglena gracilis* assay. In figure 38 the values for native B_{12} were obtained by subtracting the amount of radioactive B_{12} from the *Euglena* results. Native B_{12} was located at the end of the chromatogram, that is in TC I.

Three batches of cord serum were analyzed as described below.

Figure 39 presents an illustration of 42 ml of cord serum processed and analyzed as above, with 10 pg of labeled B_{12} added per 1 ml of serum. Native B_{12} was found both in TC I and in TC II but the region of FTC where most of the added B_{12} was located was essentially free from native B_{12} . The different regions of this chromatogram were tested for their content of TC II by CM-cellulose chromatography. In the 1 peak 69.5 % of the radioactivity was eluted from the CM-column by the final buffer. The corresponding values for B, C and D were 4.2 %, 1.5 % and 9.0 % respectively. The amounts of B_{12} in each fraction were: A 6400 pg of which 37 pg was radioactive, B 1372 pg and 106 pg, C 1408 pg and 153 pg, and D 7370 pg and

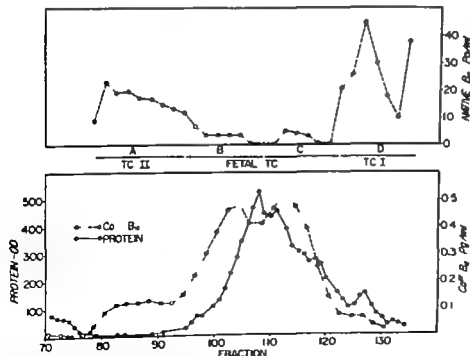


Fig 39. DEAE-cellulose chromatogram of 40 ml of cord serum with 10 pg/ml $^{57}\text{Co}B_{12}$. Fractions 1-70 were omitted from the illustration because they did not contain radioactivity.

Table 7 cont.

Exp.	Binder	Pg CoB ₁₂ applied to the cells	Number of the cells 10 ⁶	Pg ⁵⁷ CoB ₁₂ taken p per million cells	% of total CoB ₁₂ taken up
5	FTC	107.0	3.230	0	0
	FTC	109.9	3.400	0	0
	FTC	111.5	3.040	0	0
	TC I cord serum	74.6	3.000	0	0
	TC I, cord serum	74.6	3.100	0	0
	TC I, cord serum	71.6	3.150	0	0
	TC II, adult serum	121.9	3.100	1.83	4.5
	TC II adult serum	123.8	3.300	1.86	4.9
	B ₁₂ in saline	69.5	3.100	6.10	0.50
	B ₁₂ in saline	78.8	3.200	6.09	0.26
6	TC II, cord serum	11.7	3.600	0.37	4.9
	TC II, cord serum	43.1	3.100	0.34	3.9
	TC II, cord serum	48.4	3.350	0.36	3.8
	TC II, adult serum	103.3	3.100	1.44	4.0
	TC II, adult serum	107.0	2.850	1.49	5.1
	TC II, adult serum	119.0	2.000	1.60	4.0
	TC II, adult serum	41.8	0.800	0.03	0.25
	B ₁₂ in saline	42.9	3.400	0.03	0.35
	B ₁₂ in saline	42.9	3.400	0.03	0.35
7	TC II cord serum	41.9	1.300	0.29	1.5
	TC II, cord serum	41.6	1.700	0.38	1.5
	TC II cord serum	29	2.050	0.23	1.5
	TC II, cord serum	29.2	1.300	0.30	1.5
	TC II adult serum	116.7	0.800	0.44	1.7
	TC II adult serum	103.1	1.710	1.69	2.5
	TC II adult serum	34.1	2.350	0.03	0.20
	B ₁₂ in saline	43.7	1.750	0.03	0.20
	B ₁₂ in saline	43.7	1.750	0.03	0.20
8	TC II cord serum	69.6	1.750	0.86	2.3
	TC II cord serum	69.4	1.900	1.32	3.6
	TC II cord serum	69.6	1.870	1.09	2.9
	TC II cord serum	69.2	2.000	1.11	2.8
	FTC	69.8	2.100	0.003	0.01
	FTC	69.9	2.100	0.01	0.04
	T I cord serum	68.7	1.900	0.61	0.01
	B ₁₂ in saline	60.4	1.500	0.03	0.16
	B ₁₂ in saline	60.4	1.500	0.03	0.16

Table 7 *Cell uptake experiments*

Exp.	Bladder	pg $^{57}\text{CoB}_{12}$ applied to the cells	Number of the cells $\times 10^4$	pg $^{57}\text{CoB}_{12}$ taken up per million cells	% of total CoB_{12} taken up
1	TC II cord serum	33.0	1 00	0.7	1.4
	TC II cord serum	33.0	1 600	0.26	1.3
	FTC	40.7	1 600	0	0
	FTC	40.7	1 750	0	0
	B ₁₂ in saline	2.8	1.930	0.01	0.0
2	TC II cord serum	33.8	3.30	0.61	2.8
	TC II cord serum	36.0	3.500	0.30	—
	TC II cord serum	35.6	3.500	0.3	—
	FTC	98.8	3.50	0	0
	FTC	98.7	3.500	0	0
	TC I cord serum	105.1	3.700	0.06	0.14
	TC I cord serum	103.3	3.900	0.06	0.1
	B ₁₂ in saline	88.0	3.300	0.17	0.63
3	TC II cord serum	31.8	0.930	0.4	1.3
	TC II cord serum	31.1	1.000	0.33	0.83
	FTC	93.8	1 100	0	0
	FTC	93.3	1 000	0	0
	TC I cord serum	69.6	1 100	0	0
	TC I cord serum	67.8	1.000	0	0
	TC II adult serum	107.8	0.800	0.67	1.7
	TC II adult serum	116.0	0.930	0.1	1.8
	B ₁₂ in saline	88.4	0. 00	0.17	0.13
	B ₁₂ in saline	82.9	1 000	0.1	0.14
	B ₁₂ i saline	49.3	1.030	0.04	0.07
	B ₁₂ i saline	48.0	1 030	0.03	0.07
4	TC II cord serum	30.6	3.600	0.33	3.3
	TC II cord serum	36.9	3.730	0.3	7.3
	FTC	93.3	3.930	0	0
	FTC	94.8	3.930	0	0
	TC I cord serum	69.0	3.600	0	0
	TC I cord serum	73.1	3.630	0	0
	TC II adult serum	109.9	3.330	1.31	1.9
	TC II adult serum	128.8	3.330	1.6	1.3
	B ₁₂ in saline	61.8	1 630	0.03	0.13
	B ₁₂ i saline	49.8	600	0.06	0.31

Table cont.

Exp.	Bladder	pg $^{59}\text{CoB}_{12}$ applied to the cells	Number of the cells 10^6	pg CoB_{12} taken up per million cells	% of total $^{59}\text{CoB}_{12}$ taken up
1.	FTC	107.0	3,250	0	0
	FTC	100.9	3,400	0	0
	FTC	111.8	3,030	0	0
	TC I, cord serum	4.6	3,000	0	0
	TC I, cord serum	74.8	2,100	0	0
	TC I, cord serum	71.0	3,130	0	0
	TC II, adult serum	131.9	3,100	1.93	4.3
	TC II, adult serum	133.8	3,300	1.66	4.9
	B_{12} in saline	69.3	3,100	0.10	0.25
	B_{12} in saline	8.6	3,300	0.09	0.20
2.	TC II, cord serum	51.7	3,000	0.57	4.9
	TC II, cord serum	43.1	3,100	0.34	2.9
	TC II, cord serum	48.4	3,250	0.46	3.8
	TC II, adult serum	103.3	2,100	1.41	4.2
	TC II, adult serum	197.0	2,950	1.49	3.4
	TC II, adult serum	119.3	3,300	1.60	4.9
	B_{12} in saline	41.0	2,850	0.03	0.23
	B_{12} in saline	43.9	3,400	0.03	0.23
	TC II, cord serum	43.8	2,200	0.29	1.5
	TC II, cord serum	43.6	1,750	0.38	1.5
3.	TC II, cord serum	29.2	2,050	0.25	1.5
	TC II, cord serum	29.2	1,300	0.30	1.3
	TC II, cord serum	110.3	0,800	2.44	1.7
	TC II, adult serum	103.1	1,750	1.49	2.5
	B_{12} in saline	34.1	2,250	0.63	0.20
	B_{12} in saline	43	1,750	0.63	0.20
4.	TC II, cord serum	60.8	1,750	0.96	2.2
	TC II, cord serum	60.4	1,900	1.33	2.0
	TC II, cord serum	60.6	1,650	1.09	2.9
	TC II, cord serum	60.2	2,000	1.11	3.2
	FTV	60.6	1,100	0.903	0.01
	FTV	60.9	2,100	0.91	0.04
	TC I, cord serum	60.7	1,900	0.91	0.01
	B_{12} in saline	60.4	1,120	0.93	0.16

Table 8 Cell uptake experiments

Data for the uptake of CoB_{12} bound to different proteins

The results are expressed as micrograms per million cells.

TC II cord serum		TC II ad lt serum		FTC		TC I cord serum		CoB ₁₂ in ad lt serum	
Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up
18.4	0.7	159.8	.07	5.4	0	70.9	0.06	1.4	0.01
19.5	0.56	120	1	23.3	0	33.4	0.06	7.1	0.17
22.7	0.64	33.8	1.1	33.8	0	03	0	140	0.17
11.5	0.30	38.4	1.03	39.5	0	6.5	0	82.6	0.1
14	0.2	4.5	1.93	88.1	0	19	0	40.9	0.04
32.4	0.4	38.1	1.80	93.3	0	19.8	0	43	0.03
41.1	0.33	97.4	1.49	31.6	0	4.8	0	21.4	0.0
10	0.33	24.1	1.96	4.0	0	4	0	19	0.06
0.8	0.2	24.0	1.44	32.9	0	22.7	0	28.8	0.10
11.6	0.57	145.8	4.4	22.4	0	36.6	0.01	4.6	0.09
14.1	0.54	00.1	1.49	36.3	0	Mean 0.01		14.6	0.03
14.0	0.81	Mean 1.53		31	0.003	Mean 0.01		1.9	0.03
19.1	0.25	Range 1.44-07		32.3	0.01			4.1	0.03
3.0	0.38			Mean: 0.001				4.1	0.03
14.3	0.22							22.3	0.03
22.4	0.30							Mean: 0.07	
29.8	0.56							Range 0.01-0.17	
36.3	1.33								
37.6	1.09								
34.5	1.11								
Mean 0.5									
Range 0.22-1.33									

Table 9. Summary of the HeLa cell uptake experiments

Binder	Number of experiments	Uptake as pg of $^{57}\text{CoB}_{12}$ per million cells	
		Mean	Range
TC II, cord serum	20	0.52	0.22—1.23
TC II, adult serum	11	1.85	1.44—2.67
FTC	11	0.001	0—0.01
TC I, cord serum	10	0.01	0—0.06
B_{12} in saline	13	0.07	0.01—0.17

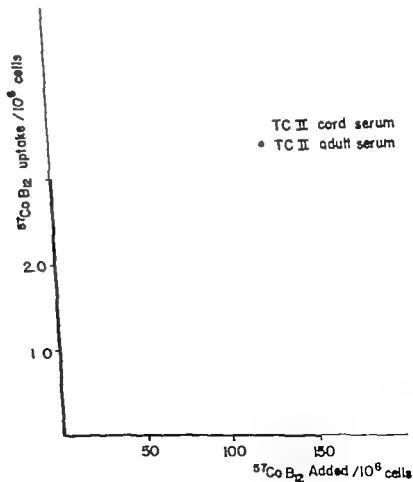
Fig. 41. HeLa cell uptake of $^{57}\text{CoB}_{12}$ from adult and cord serum TC II. The amount of CoB_{12} is expressed in picograms.

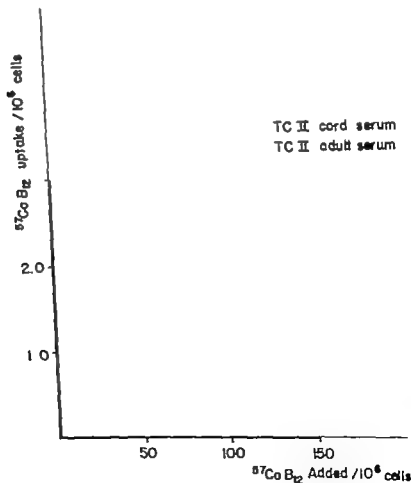
Table 8 Cell uptake experiments

Data for the uptake of $^{57}\text{CoB}_{12}$ by adult fish proteins
The results are expressed as micrograms per million cells.

TC II cord serum		TC II adult serum		FIC		TC I cord serum		TCII in red cells	
Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up
19.4	0.5	139.8	0.5	3.4	0	38.9	0.06	1.4	0.01
19.5	0.26	122.2	0.21	3.3	0	31.4	0.06	1	0.17
22.7	0.64	39.8	1.31	33.8	0	63.0	0	1.0	0.1
11.3	0.20	38.4	1.85	39.5	0	07.8	0	8.9	0.12
14.0	0.3	42.5	1.93	89.1	0	19.0	0	46.9	0.04
33.4	0.43	28.1	1.56	93.3	0	19.8	0	45.7	0.03
41.1	0.33	27.8	1.49	31.6	0	4.8	0	31.4	0.03
10.0	0.33	31.1	1.66	24.0	0	4.0	0	19.0	0.09
9.8	0.22	34.0	1.44	32.4	0	22.7	0	28.8	0.10
11.6	0.37	14.0	0.44	36.5	0	36.6	0.01	4.6	0.09
14.1	0.64	60.1	1.49	32.0	0.003	Mean 0.01		14.6	0.03
14.9	0.56	Mean 1.83		33.3	0.01	Mean 0.01		1.9	0.03
19.1	0.29	Range 1.44-6.7		Mean 0.001		Mean 0.01		4.1	0.03
25.0	0.36							20.1	0.03
14.5	0.2							32.3	0.03
22.4	0.20							Mean 0.07	
29.8	0.60							Range 0.01-0.1	
34.5	1.33								
37.0	1.00								
34.6	1.11								
Mean 0.52									
Range 0.22-1.33									

Table 9 Summary of the HeLa cell uptake experiments

Bladder	Number of experiments	Uptake as pg of $^{57}\text{CoB}_{12}$ per million cells	
		Mean	Range
TC II, cord serum	20	0.82	0.23—1.33
TC II, adult serum	11	1.83	1.44—2.67
TC I	33	0.001	0—0.01
TC I, cord serum	10	0.01	0—0.06
B_{12} in saline	18	0.07	0.01—0.17

Fig. 41. HeLa cell uptake of $^{57}\text{CoB}_{12}$ from adult and cord serum TC II. The amount of $^{57}\text{CoB}_{12}$ is expressed in picograms.

8 Table 9 gives the summary for the experiments. There was little uptake from the B_{12} -saline solution without any binders. B_{12} from complexes with FTC and TC I was only occasionally taken up and even then to an insignificant degree. TC II promoted the uptake. There was a difference between the uptake of $^{57}CoB_{12}$ from adult and cord serum TC II. Since never more than 5.4% of the total applied labeled B_{12} was taken up there was always an excess of the vitamin available to the cells. It is still possible that the amount taken up was influenced by the amount given to the cells. To study this possibility figure 41 was constructed. It gives a suggestion that this kind of phenomenon did exist while it

also shows that even at the same level of $^{57}CoB_{12}$ applied to the cells, more of it was taken up from adult TC II than from cord serum TC II. However the actual phenomenon is the uptake of vitamin B_{12} , and not that of Co-labeled B_{12} , as shown in the previous section, the amount of native B_{12} in cord serum TC II was different from that in adult TC II. The lesser uptake of $^{57}CoB_{12}$ from cord serum TC II is at least partly due to the dilution by cold endogenous B_{12} . The concentrations of native B_{12} in the fractions studied were not measured. Thus no exact comparisons can be made between adult and cord serum TC II as to the uptake of B_{12} from them.

Discussion

The binding of added B_{12} in normal adult serum

The purpose of the present work was not to make a systematic study of the phenomenon of B_{12} binding in normal adult serum. Such studies using the same methods as presented here have been published (Hall and Finkler 1965, 1966a, Hom and Oleen 1967). In this study adult samples served as a comparison for the cord serum binding pattern and as a check for the chromatographic and other techniques employed. The finding that most of the added B_{12} in normal adult serum was bound to TC II is in good agreement with the results by Hall and Finkler (1965, 1966a). The binding in some sera of added B_{12} with proteins eluted from the DEAE-column in between TC II and TC I has also been reported earlier (Hall and Finkler 1966a). This binding was thought to be nonspecific and was not explored further. This assumed nonspecificity and irrelevance to vitamin B_{12} metabolism may be correct but it is not necessary so. The binding with these proteins when subsaturation amounts of B_{12} were added may be a different phenomenon from the overflow binding found in all sera when large amounts of B_{12} were added. A systematic study on the occurrence of this type of binding has been performed earlier nor was it performed in the present work. The properties of this B_{12} -protein complex, other than its behavior in DEAE-chromatography have not been studied. This middle binder in normal adult serum will be referred to as the FTC-like binder. While there is no reason to assume that this binder might be of great importance in the metabolism of vitamin B_{12} ,

it becomes interesting when one starts comparing adult and newborn binding systems.

The work by Hom and Ahluwalia (1968) provokes further discussion concerning the possible occurrence of more than two B_{12} binders in normal adult serum. Using gel filtration on Sephadex G 200 columns, they found three binders. The third binder possessing a large molecular size, they designated TC I. Whether it has any correlation to the FTC-like binder remains to be seen. If one assumes that the FTC-like binder has the same molecular size as TC I it would be included in the TC I peak as eluted from gel filtration. This would partly explain the wide range of binding capacity attributed to TC I in the study by Hom and Ahluwalia.

The binding of added B_{12} in cord serum

The B_{12} -binding pattern in cord serum as studied by the "mini-column technique" of DEAE-chromatography is different from the adult system. This can be seen in the binding of added B_{12} to a protein, so called fetal transcobalamin (FTC) in the middle region of the chromatogram. Binding to FTC was a constant finding in the studied samples of cord serum and it occurred regardless of the amount of added B_{12} . The experiments with small amounts of added B_{12} demonstrate the difference between this phenomenon and the secondary binding to plasma proteins other than TC II and TC I after the saturation of these primary binders (Hall and Finkler 1966a). The four experiments with 1000 pg of B_{12} added per 1 ml of serum suggest that although the binding avidity of FTC is strong,

8 Table 9 gives the summary for the experiments. There was little uptake from the B_{12} -saline solution without any binders. B_{12} from complexes with FTC and TC I was only occasionally taken up and even then to an insignificant degree. TC II promoted the uptake. There was a difference between the uptake of $^{57}CoB_{12}$ from adult and cord serum TC II. Since never more than 5.4% of the total applied labeled B_{12} was taken up there was always an excess of the vitamin available to the cells. It is still possible that the amount taken up was influenced by the amount given to the cells. To study this possibility figure 41 was constructed. It gives a suggestion that this kind of phenomenon did exist while it

also shows that even at the same level of $^{57}CoB_{12}$ applied to the cells, more of it was taken up from adult TC II than from cord serum TC II. However the actual phenomenon is the uptake of vitamin B_{12} , and not that of ^{57}Co -labeled B_{12} . As shown in the previous section the amount of native B_{12} in cord serum TC II was different from that in adult TC II. The lesser uptake of $^{57}CoB_{12}$ from cord serum TC II is at least partly due to the dilution by "cold" endogenous B_{12} . The concentrations of native B_{12} in the fractions studied were not measured. Thus no exact comparisons can be made between adult and cord serum TC II as to the uptake of B_{12} from them.

this PTC-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to PTC and some parameter of fetal-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the PTC-like binder to learn whether it is FTO or not.

As to the correlation of the binding to PTC in maternal blood with the degree of binding to PTC in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however, interesting to note that in the case of slight binding to PTC at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 19

Characterization of the B_{12} binders in cord serum

In DEAE-chromatograms of cord serum a binder corresponding to TC I was found. Further characterization of it by the methods used failed to detect any differences between it and adult TC I. It was shown to be the carrier of native B_{12} and to bind little of the added B_{12} . It behaved the same as adult TC I in the CM-cellulose chromatography system. Its electrophoretic mobility was in the fast globulin region and it had a molecular size corresponding to a molecular weight of about 130,000. It did not deliver its bound- B_{12} to HeLa cells. All the above features are the same as those described for adult TC I (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom and Olsen 1967).

A binder corresponding to TC II was also found in cord serum. It had the same behavior in the CM-cellulose chromatography system, and it had the same electrophoretic mobility as adult TC II. It had a molecular size which was smaller than that of albumin. It caused

a considerable uptake of B_{12} by HeLa cells, when the vitamin was introduced to the cells bound to it. The main difference between this binder and adult TC II was the content of native B_{12} in cord serum TC II. This phenomenon has not been described earlier for adult TC II (Hall and Finkler 1965, Gabunda *et al.* 1965). However a personal communication with Hall (1967) after the completion of the present experiments has given supporting evidence for the possible occurrence of native B_{12} in TC II in some samples of adult serum. Further studies on this are underway. Thus the difference between adult and cord serum TC II may be more quantitative than qualitative. The occurrence of native B_{12} in cord serum TC II also explains the other found difference: the decreased uptake of $^{57}\text{CoB}_{12}$ by HeLa cells from cord serum TC II as compared to adult TC II.

The finding that TC II may contain native B_{12} contrary to the earlier concept is by no means revolutionary when considering its function. TC II is known to bind newly introduced B_{12} both *in vivo* and *in vitro* and further deliver it to the cells and tissues (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom 1967b, Betief *et al.* 1967b). If the balance between taking up B_{12} and delivering it to the tissues is in favor of the former B_{12} will no doubt accumulate in TC II. It is not known whether it is an increased uptake or decreased delivering of B_{12} which makes cord serum TC II contain native B_{12} . Some difference in TC II itself is not excluded, but nothing in the present study favors such a concept.

The "new" B_{12} binder, the so called fetal transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently in DEAE-chromatograms of adult serum, but it has not been characterized further. It may be the same binder and can be called the FTO-like binder. In the present study the basic difference between PTC and the other

its capacity is limited. The present data does not answer the question of whether the difference between adult and cord serum binding patterns is qualitative or quantitative, i.e. whether FTC is the same as the FTC-like binder in the chromatograms of some adult sera

The binding of added B₁₂ in infant serum

In order to obtain information about the origin and disappearance of FTC infants of different ages were studied. There was a tendency towards less binding of added B₁₂ to FTC in older infants, but the changing pattern was far from clear-cut. If FTC had its origin outside the infant, that is in the placenta or in the mother it would disappear at the same rate in each infant, depending on the turnover of the protein molecule. The inconsistent rate of disappearance indicates that FTC has its origin in the infant itself. It remains to be explained, why in one infant at the age of 10 days an adult binding pattern exists, and in another at the age of 106 days a considerable amount of the added B₁₂ is bound to FTC. The possible factors which could have an influence on this phenomenon are the B₁₂ concentration in the serum and the amount of it bound to TC. If i.e. the saturation of the other binders. These things were not studied in the present work. Also to be considered is the fact, that even in normal adult serum there are differences as to the amount of added B₁₂ bound to an FTC-like binder. The factors influencing this phenomenon are equally unexplained.

To study serial successive samples from the same infants is very informative in solving the problem of changing B₁₂ binding pattern. Obtaining this kind of material is naturally difficult, and the limited material presented here should be reviewed in this light. No definitive information concerning the disappearance of FTC could be obtained from this material. It does suggest that binding to FTC

diminishes during the first few weeks of life. This could very well reflect the gradual disappearance of FTC from the serum, although the amount of added B₁₂ being bound to FTC does not necessarily parallel the concentration of FTC. Various factors, such as the saturation of other B₁₂ binders, may play a role in the distribution of added B₁₂ between the binders. Adding labeled B₁₂ is, however, the only approach to FTC since there are no means of measuring its actual concentration.

In all the studied samples which were either cord serum or serum drawn from infants during the first week of life FTC occurred as one of the principal binders of added B₁₂, and the binding pattern was distinctly different from the adult binding pattern.

The binding of added B₁₂ in maternal serum

The analyzed maternal serum samples did not give a clear-cut answer to the question concerning the existence or non-existence of FTC in the delivering mother. Three of the samples were definitely of the adult type and five more could fit the adult pattern with some binding of added B₁₂ to an FTC-like binder. However four of the samples remained in the category of "abnormal binding to an FTC like binder".

One possible explanation for the occurrence of FTC in the maternal circulation is that FTC is of fetal origin and may be carried over to the maternal side by a feto-maternal hemorrhage which is known to be a relatively common phenomenon (Cohen *et al* 1964). Such a hemorrhage is usually of a minor degree and thus the amount of FTC entering the maternal circulation would be very small. It could, however, play a detectable role in the binding of added B₁₂ if one assumes that the binding avidity of FTC for B₁₂ is strong. A study of serial samples from mothers with

this FTO-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to FTO and some parameter of feto-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the FTO-like binder to learn whether it is FTO or not.

As to the correlation of the binding to FTO in maternal blood with the degree of binding to FTO in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however, interesting to note that in the case of slight binding to FTO at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 10

Characterization of the B_{12} binders in cord serum

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The new B_{12} binder (the so called fetal transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently in DEAE-chromatograms of adult serum, but it has not been characterized further. It may be the same binder and can be called the FTC-like binder. In the present study the basic difference between FTO and the other

binders, TC I and TC II is its different behavior in DEAE-cellulose chromatography. This can be explained by the differences in the electric charge of the molecules. These same differences are further reflected by electrophoretic mobilities. FTC has an intermediate mobility when compared with TC I and TC II and is mobility similar to α globulins when compared with serum proteins. In the CM-cellulose chromatography system used FTC behaved like TC I and was eluted from the column by the starting buffer. As to the molecular size it was similar to that of TC I i.e. its molecular weight is approximately 120,000. FTC thus forms one peak with TC I when labeled serum is fractionated by gel filtration in Sephadex columns. When

CoB₁₂ bound to FTC was incubated with HeLa cells, there was no uptake by the cells. In this respect too, FTC behaves like TC I. The main difference between TC I and FTC besides the differences in the electric charge is the non-content of native B₁₂ in FTC.

Finkler *et al* (1968) showed that FTC reacts with an antiserum produced against TC I from leukemic blood and with an anti serum against the salivary R-binder but not with an antiserum against TC II. FTC thus seems to be immunologically similar to TC I and to belong to the "R-group" of B₁₂ binders, which includes TC I and B₁₂ binders in gastric juice, saliva, bile, cerebrospinal fluid and blood cells (Simons 1964, Stenman *et al* 1967, Grasbeck 1967). Immunological properties, molecular size behavior in HeLa cell culture and in the used CM-cellulose chromatography system all link FTC to the "R-group" of B₁₂ binders. The B₁₂ binding protein in human milk (Finkler *et al* 1967) may belong to "R-group" as well although immunological evidence is lacking. Stenman and co-workers (1968) showed that the "R-binders" of different origin differ as to their molecular electric charge. They ascribe this to the differences in sialic acid contents. The same concept may apply to FTC.

What then is the role of FTC in the previously well-organized family of serum B₁₂ binders? It is clear that it does not share the carrying of native B₁₂ with TC I. The *in vitro* studies indicate that it has the same properties as previously described for TC II, i.e. not containing B₁₂ but being able to bind added B₁₂. However, TC II has been shown both *in vivo* and *in vitro* to deliver its B₁₂ to cells and tissues (Hall and Finkler 1966, Finkler and Hall 1967, Hom 1967b). No such function for FTC was demonstrated by the present HeLa cell culture studies. This does not rule out the possibility that FTC could, under different circumstances or with other types of cells, act as a carrier of B₁₂ to body cells. The B₁₂ uptake from the binders has been shown to be tissue specific by experiments using intrinsic factor and the R-binders of serum, leukocytes and gastric juice (Simons *et al* 1966). It was shown that guinea pig intestine homogenate took up B₁₂ from intrinsic factor complex but not from R-binder complex, whereas the reverse was true for rat liver homogenate. These studies were performed using heterologous systems which reduces their value. It should also be noted here that in the work cited above the serum R-binder equals TC II. To get a firmer basis for the speculation concerning the function of FTC would necessarily require *in vivo* studies.

It is interesting to note that there is one serum B₁₂ binder which resembles FTC in all its studied properties. This is the B₁₂ binder in polycythemia vera serum (Hall and Finkler 1967). It does not carry endogenous B₁₂ but binds added B₁₂. Its behavior in DEAE and CM-cellulose chromatographies is the same as that of FTC: it has an intermediate electrophoretic mobility when compared to TC I and TC II and it has a large molecular size. It does not promote the uptake of B₁₂ by HeLa cells. Furthermore the polycythemia vera binder reacts with an antiserum produced against TC I (Finkler *et al* 1968). It is an interesting analogy that in some cord and

neonatal sera and in a small number of maternal sera immediately after delivery a protein which was antigenically similar to a protein found in some malignant diseases, has been detected (Takahashi *et al* 1967). This protein has no known correlation with vitamin B₁₂.

A starting point for the present work was the difference in B₁₂ concentrations between cord serum and maternal serum. The most interesting result of the experiments was the description of a new B₁₂ binder which is

called FTC. It does not give any explanation for the difference in B₁₂ serum concentrations, because it does not contain native B₁₂. The possible explanation for the initiating problem could be the native B₁₂ found in cord serum TC II. This aspect was not explored further since with the discovery of FTC the work was focused on the characterization of it. Whether FTC has anything to do with the transplacental passage and concentration gradient of vitamin B₁₂, remains to be elucidated by further work.

Summary

The serum binding of vitamin B₁₂ in the newborn infant was studied using *in vitro* labeling of serum proteins with ⁵⁷CoB₁₂ and ionic exchange chromatography for the separation of B₁₂ binders. As to the carrier of native B₁₂ TC I no differences were found when adult and cord sera were compared. For the binder of exogenous or new B₁₂ TC II one previously unreported phenomenon was detected in cord serum. TC II was found to contain native or endogenous B₁₂. A third B₁₂ binder which was designated fetal transcobalamin or FTC was found in cord serum. FTC did not contain native vitamin B₁₂ but it bound *in vitro* added vitamin B₁₂. FTC had the same molecular size with TC I (molecular weight around 120 000) and its electro-

phoretic mobility was between TC I and TC II at pH 8.6 and pH 4.5. ⁵⁷CoB₁₂ bound to FTC was not taken up by HeLa cell cultures. The studied serum samples from infants did not permit any definite conclusions about the "normalization" of the newborn B₁₂ binding pattern although binding of added B₁₂ to FTC diminished with age. Part of the studied maternal sera contained a binder similar to FTC as judged by DEAE-chromatography. The possible similarity between FTC and a minor binder in some adult sera was discussed. A suggestion was made that FTC belongs to the "R-group" of B₁₂ binders by the terminology of Simons (1964). No specific function for FTC could be clarified by the present *in vitro* studies.

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PÆDIATRICA
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**GROUPS AT RISK IN LOW BIRTH
WEIGHT INFANTS
AND PERINATAL MORTALITY**

BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL, STOCKHOLM SWEDEN

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GROUPS AT RISK IN LOW BIRTH
WEIGHT INFANTS
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BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

GROUPS AT RISK IN LOW BIRTH WEIGHT INFANTS AND PERINATAL MORTALITY

A prospective study of the biological characteristics and socio-
economic circumstances of mothers in 12,000 deliveries in North
Finland 1966

A discriminant function analysis

By
Paula Rantakallio

Translated by
Hilkka Kontiopää
Valerie Jansen

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Printed in Finland
KIRJAPAINO OSAKEYHTIÖ KALEVA
Oul 1969

Introduction

Infant mortality that is mortality during the first year of life, has fallen dramatically in all advanced countries in the last thirty years. Neonatal mortality that is mortality during the first few weeks of life, has also fallen, but considerably more slowly. As a result, the proportion of neonates in infant mortality has increased and now amounts to approximately two-thirds.

This trend has everywhere stimulated investigation into the etiology of neonatal mortality and efforts to reduce it.

Most deaths within the first 24 hours of life occur as a result of intrauterine or intranatal factors, as in stillbirths. Clifford states

What kills a baby ten minutes before birth, is probably the same factor that kills it ten minutes after birth. (28) The term *perinatal mortality* was coined to cover the mortality of the foetal period and neonatal period combined.

The perinatal mortality rate not only reflects the number of deaths during this period but should also be understood as a measure of health care, closely connected with the health of the surviving children. Nixon wrote: The perinatal death rate is also an index of the number of near-deaths which may have occurred. Like an iceberg, we see only a proportion of the ill-results, the deaths. But we must not forget the submerged and larger fraction, the near-deaths and the harm which they cause. The correlation is suggestive, because some causes of death — premature delivery asphyxia during labour Rhesus incompatibility — are known to be associated with the occurrence of mental and physical defects in some of the survivors. With reduction in perinatal mortality there will also

follow *pari passu*, a diminution in perinatal morbidity (103)

Premature, or low birth weight infants are the most important group in perinatal mortality in various surveys they comprise 50-70 per cent of this mortality. Prematurity was first given attention in 1919 by Ylppö (172) who suggested the group limit of a birth weight of 2500 grams which is still in use. Efforts have, however been made to find increasingly accurate criteria to determine the limit of risk groups versus non-risk groups, and increasing attention is being focused on the gestational age, as well as birth weight.

The mean birth weights of populations from different geographical districts show remarkable differences, a fact which is partly reflected in the frequency of low birth weight infants. There are also regional differences in the mean gestational length and therefore a determination and detailed analysis of risk groups in the light of these two characteristics requires basic information about each population.

Despite progress in the intensive care of the newborn, the results are as yet far from satisfactory. On the other hand, obstetric help often comes too late, after the foetal death has already occurred. It would be better to give mothers of risk group infants intensified prenatal care as soon as pregnancy has started and intensive obstetric therapy in good time. The vast majority of pregnancies culminate in the birth of a healthy infant, and the problem is how to identify early in pregnancy from a large population of parturients those whose infants are likely to belong to a risk group.

Purpose of the present study

- 1 To analyse the variations in and correlations of birth weight and gestational age in the present series
- 2 To determine the correlation of perinatal mortality with birth weight and gestational age
- 3 To find out the possible correlations between birth weight and perinatal mortality with the mother's biological characteristics and socio-economic circumstances.
- 4 To study how and to what extent, the child's birth weight and risk of perinatal mortality can be predicted early in pregnancy from the mother's biological characteristics and socio-economic circumstances.

In order to identify risk-group mothers more knowledge is needed about the factors influencing birth weight and gestational age. It is known from many earlier studies that low birth weight and variations in perinatal mortality are closely connected with the mothers biological characteristics (e.g. age, parity height weight general health) On the other hand, there is also known to be a

correlation with the mothers social and economic circumstances, and there may equally well be a causal connection with the mothers environment (e.g. rural or industrial) and the public health services available Birth weight and perinatal mortality are typical variables in human biology and can only be judged in the context of the total environment.

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Review of the literature

Determination of risk group criteria on the basis of the child's characteristics

In his study of 1919 Yipso suggested a classification of prematurity based on birth weights under 2500 grams (172). This criterion indicative of abnormal immaturity was gradually accepted in general practice. The American Academy of Pediatrics recommended it in 1935 and WHO in 1948 (168).

Since the early 1950s, increasing attention has been given to gestational age and birth weight combined in the determination of the child's maturity and chance of survival (27, 45, 67, 73, 77, 91, 129, 137, 141). It has clearly emerged from these studies that not all children with a birth weight under 2500 g were premature in view of gestational age. WHO recommended in 1961 that the term 'premature' be abandoned in connection with children with a birth weight under 2500 g and replaced by the term 'low birth weight infant' (169).

Since the child's risk of death has been related to the twin factors of birth weight and gestational age, attention has also been devoted to children whose birth weight falls outside the range of distribution considered as normal, calculated separately for each gestational age group. Gruenwald used standard deviations to measure this distribution (57), allotting a plus and minus score based on the standard deviation with a rating between 0— -2 for birth weights lower and 0— +2 for those higher than in normal cases (59). Lubchenco was the first, in 1963 to present the distribution of birth weights by percentiles (86) and this custom has been

generally accepted (14, 24, 38, 62, 87, 102, 108).

In the light of these studies it seems increasingly apparent that both the mortality (14, 16, 21) and morbidity (16, 30, 66, 89, 130, 160, 161) rates vary in children of equal weight but of different gestational age. For this reason efforts have been made to create methods of appraisal by which the degree of foetal development, i.e. gestational age, can be determined with the greatest possible accuracy from the various biological characteristics of the newborn (80, 94, 100, 152).

The mother's biological characteristics, socio-economic and other environmental circumstances

There is a very extensive literature on maternal biological characteristics and socio-economic status, and on regional factors pertinent to perinatal mortality and low birth weight. Reference may be made here to an excellent general survey recently published on the factors contributing to low birth weight in the newborn (4—6).

Community studies in relation to birth weight and perinatal mortality

McKeown and Gibson carried out an investigation of 23 970 births in Birmingham in 1947 calculating perinatal mortality according to the gestational age, birth weight and sex of the child and analysing the correlation of birth weight with maternal age, parity and socio-economic circumstances (53—55, 90—92).

Shapiro compared two parturient populations in New York in 1955—57 with regard to perinatal mortality and frequency of low birth weight, focusing his attention on the different levels of the medical care available to these groups (132, 133).

The British Perinatal Mortality Survey is the most extensive study in this field (21). It covers 16,994 births in Great Britain during one week in 1958 plus 7 117 perinatal deaths in a three month period. Information was collected on the mothers biological characteristics and socio-economic circumstances, general health and medical care during pregnancy, obstetric help, and postmortem diagnoses of the dead infants.

In addition, there are several perinatal studies in progress, among them The North Carolina Study of Fetal and Neonatal Deaths (26), a combined project of several hospitals, with the results published in a series of publications (1—3 36, 56, 118 163).

Use of multi-variable analyses

The etiology of perinatal mortality and low birth weight is typically multi factorial. In the 1960s their study with the aid of multi-variable analysis has become increasingly popular (1—3 40 41 56).

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Since the child's risk of death has been related to the twin factors of birth weight and gestational age, attention has also been devoted to children whose birth weight falls outside the range of distribution considered as 'normal', calculated separately for each gestational age group. Gruenwald used standard deviations to measure this distribution (57), allotting a plus and minus score based on the standard deviation with a rating between 0— -2 for birth weights lower and 0— +2 for those higher than in normal cases (59). Lubchenco was the first, in 1963, to present the distribution of birth weights by percentiles (86) and this custom has been

generally accepted (14 24 38 62, 87 102, 108).

In the light of these studies it seems increasingly apparent that both the mortality (14 16 21) and morbidity (16 30 66 89 130, 160 161) rates vary in children of equal weight but of different gestational age. For this reason efforts have been made to create methods of appraisal by which the degree of foetal development, i.e. gestational age can be determined with the greatest possible accuracy from the various biological characteristics of the newborn (80 94 100 152).

The mother's biological characteristics, socio-economic and other environmental circumstances

There is a very extensive literature on maternal biological characteristics and socio-economic status, and on regional factors pertinent to perinatal mortality and low birth weight. Reference may be made here to an excellent general survey recently published on the factors contributing to low birth weight in the newborn (4—6).

Community studies in relation to birth weight and perinatal mortality

McKeown and Gibson carried out an investigation of 23 970 births in Birmingham in 1947 calculating perinatal mortality according to the gestational age, birth weight and sex of the child and analysing the correlation of birth weight with maternal age, parity and socio-economic circumstances (53—55 90—92).

review there were 66 local physicians working in the district. There were 373 obstetric beds in the district's 33 hospitals, 28 of the hospitals were supervised by the local physicians, while 5 with a total of 173 beds, were run by 7 specialized obstetricians and gynaecologists. There were 11 pediatricians in the district in that year. On per cent of the deliveries of the present survey occurred at home, the same percentage as for births in 1966.

Before the study proper was launched, a pilot study was carried out in the district, and the questionnaire was designed on the basis of the information obtained. Local midwives were informed of the purpose of the study of how to complete the questionnaire and how to interview the patients, by means of circular letters and meetings. While the information was being collected they could get in touch with the author at any time.

The study covered all the live born and stillborn infants with birth weights of 600 grams or more.

Information was available on 12,068 births. Stillbirths and infants who died before the age of 28 days totalled 316. According to the central Office of Statistics, births in this district during 1966 totalled 12,527 of which 330 died in the perinatal period (159). Although the present study does not exactly

cover the year 1966, the figures can be compared to see whether information on all births was collected. The present series comprised 96.3 per cent of all births in 1966, and the present figure for perinatal deaths is 95.8 per cent of the relevant mortality in 1966. The present series had 13 fewer stillbirths, and 1 neonatal death less than was recorded by the Central Office of Statistics figures for 1966. Statistics on the frequency of low birth weight are kept in Finland by the National Medical Board, which collects the data from antenatal clinics and from hospitals. Live births with birth weights of 601–2500 grams in 1966 in the district of the present study totalled 540 (112) while the present series comprised 524 hence the total of low birth weight infants is 97.0 per cent of the relevant 1966 figure.

The information collected contained 163 twin births which were excluded from the study. There were 11 905 single births. Table 1 shows these distributed into low birth weight infants with a birth weight under 2500 g, and those with birth weights of or exceeding 2500 g, giving the mortality rates of the different phases of the perinatal period per group. All infants of a gestational age between the beginning of the 38th and the end of the 42nd gestational week have been considered as term births. Pre-term births were taken

TABLE 1 Distribution of the present series of cases by low birth weight and by perinatal mortality

Mortality during perinatal period	Birth weight 2500 g or more		Birth weight less than 2500 g		Total	
	Number of cases	Rate per thousand	Number of cases	Rate per thousand	Number of cases	Rate per thousand
Stillbirths	70	6.1	90	182.7	160	13.44
Died at 0–7 day	39	3.4	69	138.3	108	9.07
Died at 8–28 days	10	0.9	5	10.0	15	1.26
Total mortality	119	10.4	164	329.7	283	23.77
At the end of perinatal period	11,267	989.6	335	671.3	11,622	976.23
Total	11 406	1000.0	499	1000.0	11 905	1000.00

Material and method

The material comprised all the births in the provinces of Oulu and Lapland — the most northerly parts of Finland — over one year. These provinces cover 160 000 sq km., which is about 48 per cent of the total area of the country. The population is roughly 604 000 of whom some 204 000 are urban dwellers. The majority of the population are Finns though there are also some 3,500 Lapps. The district is situated at 63°30'—70°0' North and 21°0'—30°31' East. The mean temperature in January is -12°C below zero and in July +15°C. Daylight in December averages 2 hours and in June 23 hours per day. Fig. 1 shows the area from which the data were collected.



Fig. 1 Area within which data were collected

Since the study was prospective, inclusion in the survey was determined by the calculated term: the series comprised all the mothers in this district with calculated term falling between January 1—December 31, 1966. A small percentage of the births in fact occurred towards the end of 1965 and early in 1967. The calculated term, as is customary, was counted from the first day of the last menstrual period. Where this date was unknown the expected term was estimated from the date of commencement of foetal movements and progress of the pregnancy.

Information on the mothers was collected by the antenatal clinics on a questionnaire. The data used for the study are presented in Appendix I. Efforts were made to obtain this information in the 24th to 28th gestational week, but where this failed the questionnaire was completed later in the pregnancy or after the delivery. Information on the child's date of birth, birth weight, death, illness, etc., is forwarded by maternity homes to the antenatal clinics which enter it on their files. Information on the child up to the age of 28 days was obtained at the mother's follow-up examination in maternity clinics.

The data was collected at the 157 antenatal clinics of the district by the 188 local midwives who have a two-year period of training and work under the local urban and rural physicians who also take part in antenatal clinic work. Legislation providing for the setting up of antenatal and child clinics by local authorities has been in operation in Finland since 1944. The local authorities are under a legal obligation to arrange free examinations at the clinics for pregnant mothers and their newborn children. In the year under

in a group length of gestation unknown. No other criteria were used to determine the gestational weeks. The expected date determined by the antenatal clinics was not corrected with the exception of a few cases in which a check was made to make sure that the dates had been correctly written.

Information on the child up to the age of 28 days was nearly always easy to obtain. Those moving from the district were traced either by the network of antenatal clinics or by social welfare authorities. In only five cases was the child lost sight of after the first week of life.

In the analysis of the data, the following groups were used: (1) perinatal deaths, (2) birth weight under 2500 g, (3) gestation of 37 weeks or less, and (4) gestation of 43 weeks or more. A pseudo-random computer sample of 1,000 cases was taken of the total of 9 974 cases (Table 2) of term infants living at the end of the perinatal period and those of unknown gestational age; the sample was based on the serial numbers printed on the questionnaires. This group of 1,000 will be termed *controls*. Whenever results were to demonstrate the distribution of the total material the correction coefficient (inverse number of the sampling ratio), to avoid decimals, was 10 instead of 9 974 which is of no importance in the results. The number of cases in the total series, therefore, is given as 11 931 instead of 11 905.

The data on mothers were entered on the questionnaires of 92 per cent of the cases prior to delivery. A study of the completion of questionnaires for low birth weight infants, dead infants and controls revealed differences between the groups. The questionnaires for dead infants with birth weights of 2500 g or more were completed almost as often before birth as those for the controls, whereas those for low birth weight infants were more often completed after birth, especially among the dead infants of this group (29.9 per cent).

When the questionnaires were analysed for absence of individual data, it was again found

that the data for the controls were most complete and those for the dead low birth weight infants least complete. The figures below show the number of questions that had a given percentage of answers missing in the two groups.

	Less than 5 per cent	5.1-10 per cent	10.1-15 per cent	Total questions
Controls	36	10	1	47
Low birth weight, deaths	25	14	8	47

The questions concerning the mother's age, marital status, parity, abortions and place of residence were answered on practically all forms (answers were missing on less than 0.8 per cent of questions). For deaths and low birth weight infants, missing information was later traced from antenatal clinic records concerning previous low birth weight infants and previous perinatal deaths. For this reason the information is less complete on this point in the control group: thus no reply was given to the former question in 10.7 per cent and to the latter in 7.1 per cent, as against 3.7 and 2.4 per cent for the perinatal deaths of low birth weight infants. For questions on deaths and low birth weight infants that were initially not answered and later answered from clinic records and otherwise, it appeared that questions requiring a negative answer had been answered less often than those requiring a positive answer.

All calculations were made by computer. The variation of the birth weight and gestational age, and the relationship of perinatal mortality to them were calculated by the customary statistical methods. The other two questions studied correlation of perinatal mortality and birth weight with the mother's biological characteristics and socio-economic circumstances, and the prediction of perinatal mortality and birth weight from the biological characteristics and socio-economic circumstances at the beginning of pregnancy were combined, Fisher's discriminant function analysis being used in the calculation (44). The purpose of the analysis was to find the linear

TABLE 2. *Distribution of survivals at the end of perinatal period into pre term term and post term births Low birth weight infants and those with birth weights of 2500 g or more are shown separately*

Birth weight g	Gestation 37 weeks or less	Gestation 38-42 weeks	Gestation 43 weeks or more	Length of gestation not known	Total
2500 g or more	696	9 615	617	359	11,287
Less than 2500 g	191	121	6	17	335
Total	887	9,736	623	376	11 622

TABLE 3 *Distribution of perinatal deaths into pre term term and post term births Low birth weight infants and those with birth weights of 2500 g or more are shown separately Mortality rates per thousand are calculated from the relevant distributions of the total number of cases*

Birth weight g	Gestation 37 weeks or less	Gestation 38-42 weeks	Gestation 43 weeks or more	Length of gestation or known	Total
2500 g or more					
— number	25	79	11	4	119
— mortality per thousand	34.7	8.1	17.5	11.0	10.45
Less than 2500 g					
— number	123	25	2	14	164
— mortality per thousand	391.7	171.2	250.0	451.6	328.66
Total					
— number	148	104	13	18	283
— mortality per thousand	143.0	10.7	20.4	45.6	23.77

as those prior to the beginning of the 38th gestational week and *post term* those whose 43rd week had commenced. The gestational age is indicated in terms of weeks that had begun. For example, the 40th week refers to 274—280 days calculated from the first day of last menstrual period. Table 2 gives the distribution of the 11 622 survivals at the end of the perinatal period by gestational age into pre-term term and post term infants, and those of unknown gestational age. Table 3 gives the corresponding figures for the 283 infants who died in the perinatal period with mortality rates.

Since inclusion in the present survey was decided at the antenatal clinic, the length of gestation was calculated according to the calculated term and the actual date of the

child's birth. In a large number of cases the calculated term was determined by a method which in some months of the year made the expected date 1—3 days late. Should pregnancies start uniformly on the different days of the year the expected date of delivery calculated by this method would be on average 0.76 days late.

Birth weight was recorded on the questionnaire in the usual way within 5 grams either way whereas truncated 100 gram class limits were used in all calculations. For example weight group 1500 g comprised birth weights of 1500—1599 grams.

The birth weight was known in every case. Cases in which the expected date of delivery could not be determined according to the first day of the last menstrual period were placed

The calculations for discriminant function analysis were carried out with an Elliott 803 computer. Group dispersions, group means, group covariances and group correlations of the variables were calculated. The pooled covariance matrix of the groups was calculated, the characteristic equation was solved and the eigenvector for each pair of groups to be discriminated was determined (32). The significance of the individual discriminant functions was studied by means of Rao's chi square approximation (116). The next step was to calculate the correlations of the discriminant, group means and group dispersions.

Lastly a classification to decide the group membership of each individual was calculated by means of the parameters already obtained, and they gave the discriminant score and probability for each case. The discriminant scores indicate the point of each case in discrimination space. The probability of membership in either of the two groups was calculated according to the distances between

the point the case had obtained in discrimination space and density of the groups (32, 81). Since the figures involved were calculated from the mothers' characteristics, the probability of a mother being in a particular group indicated the extent to which the relevant mother's characteristics corresponded to the typical characteristics of the group. Any cases in which the variables used are known can be classified by this method, as well as the cases involved in the present analysis. In the present study the total number of cases was classified on the basis of the probability classification of analysis A. The true low birth weight rates were used as a criterion to measure the effectiveness of the above probability classification.

According to the result of the classification, the present data were divided into identifiable risk groups of varying degree, and the characteristics of the infant and mother in these groups were studied.

multi variable combination which best discriminates the studied risk groups from control group and on this basis to form a function for classification to help define for individual cases the probability that they belong to a particular group

The object of the study was to pick out those mothers whose pregnancy ran a risk of perinatal mortality or low birth weight. The hypothesis was moreover that perinatal deaths do not form a uniform group but that the low birth weight deaths make up a group different from those with birth weight of 2500 g or more for this reason the discriminant analysis was carried out with 3 pairs of groups. Every analysis involved 2 groups, one consisting of 1000 control cases while the other represented a risk group. The risk group was selected as follows

Analysis	Risk group	Number of cases in risk group
A	Birth weight less than 2500 g, all cases	499
B	Birth weight less than 2500 g, deaths only	164
C	Birth weight 2500 g or more, deaths only	119

The risk group of analysis A thus contained that of analysis B which was one-third of the former

Since the discrimination score obtained by the analysis is a linear combination of the variables used the effect of individual variables in the discrimination depends on the other variables used and in another context the effect of the variables might be different. For this reason the pairs of groups used in analyses A and B were also analysed with a different combination of variables. The analyses A, B and C had 43 variables, the same in all these analyses. The groups of analysis A 1 were those of analysis A and the groups of analysis B 1 those of analysis B, but the number of variables in A 1 and B 1 was 27 of which 23 were also involved in analyses A and B. Appendix 1 presents the variables

of the multiple discriminant analysis and Table 10 shows (see page 23) the variables used in each analysis

All variables were characteristic of the mothers and their sphere of life and none of them concerned the course of the pregnancy, the delivery or the child. Lorn Analyses A 1 and B 1 included however two variables which measured attitudes during pregnancy. The variables were classified according to their information content, and the classification is presented below even though the class limits were often approximate and a short definition of all information content was difficult

Classification	Variables
Biological characteristics	1-8
Socio economic circumstances	9-47
Social standing	9-16
Conditions in childhood	17-20
School attendance and intellectual interest	21-22
Attitudes to pregnancy and to help by public authorities	23-25
Smoking	26
Work	27-33
Housing standards	34-37
Standard of living	38-39
Internal migration, and particulars of the current and possible earlier place of residence	40-47

The mathematical theory on which the multiple discriminant analysis is based presupposes that the variables used are continuous and normally distributed. Not all the variables present fulfilled these conditions. The influence of such variables on a discriminant analysis is not known in detail.

Since information on every variable was not available for all the cases, a correction programme was used for the analyses: the missing observation was replaced by a random value according to the distribution of the relevant variable in each group. The missing observations for control cases were corrected according to the distribution of the controls, those for the low birth weight cases according to that of the low birth weight infants, etc.

The calculations for discriminant function analysis were carried out with an Elliott 803 computer. Group dispersions, group means, group covariances and group correlations of the variables were calculated. The pooled covariance matrix of the groups was calculated, the characteristic equation was solved and the eigenvector for each pair of groups to be discriminated was determined (32). The significance of the individual discriminant functions was studied by means of Rao's chi square approximation (116). The next step was to calculate the correlations of the discriminant, group means and group dispersions.

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Results

1 Variations in and correlations of birth weight and gestational age

The series comprised 32.7 per cent primiparas, 24.1 per cent parity 2, 14.3 per cent parity 3, 10.5 per cent parity 4, and 18.4 per cent parity 5 or more.

Of the infants born whose sex was indicated 6,195 (52.1 per cent) were boys and 5,702 (47.9 per cent) girls, which gave a sex ratio of 1086 boys per 1000 girls. In 34 instances the sex was not indicated. The arithmetic means and standard deviations of birth weight, length at birth and gestational age were as follows:

	Girls	Boys	Total
Birth weight, g			
Mean	3382	3500	3444
S.d.	539	590	569
Length at birth, cm			
Mean	49.9	50.5	50.2
S.d.	2.3	2.6	2.5
Gestational age, days			
Mean	278.0	276.9	277.4
S.d.	15.0	15.0	14.9

The birth weight and gestational age of all cases are cross-indexed in Table 27 (Appendix 2) in class intervals of 100 g weight and 1 week. Fig. 2 shows the distribution of birth weights by 100 gram weight groups. The most common weight group is 3600 grams (8.4 per cent) and 25.0 per cent fall within the range of 3500—3799 grams.

Mean birth weights per gestational week were expressed both by the arithmetic means and medians and intrauterine growth curves were plotted for both. The 10th, 25th, 50th, 75th and 90th percentiles are presented in Tables 4 and 5. The smoothed values were calculated using polynomial regression of degree 3. The median values up to the 34th gestational week were slightly lower and after the 34th week slightly higher than the arithmetic means of the birth weights. The 10th and 90th percentile curves calculated by different methods agree fairly well from the 34th gestational week onwards. For the purpose of the comparisons in the present study

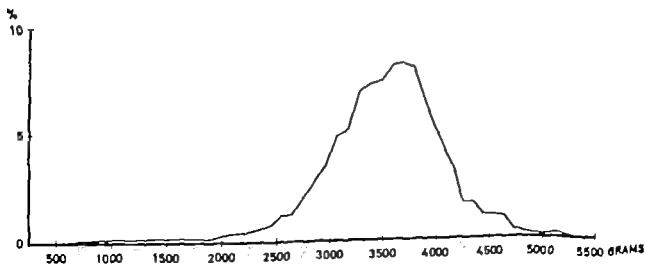


Fig. 2 Percentage distribution of the total number of cases in 100 gram weight groups

TABLE 4 Mean values of birth weights in the 25th—46th weeks of gestation and the percentile values calculated from them. Total series of cases

Gestation, weeks	Number of cases	Mean	Smoothed values					
			%	10 %	25 %	50 %	75 %	90 %
25	6	900		450	700	955	1190	1410
26	11	1150		440	730	1050	1360	1635
27	13	1120		490	810	1180	1540	1860
28	13	1230		570	930	1340	1730	2095
29	13	1510		690	1080	1510	1940	2330
30	24	1550		850	1230	1700	2130	2555
31	30	1760		1030	1450	1910	2360	2780
32	24	2250		1240	1660	2120	2580	2990
33	65	2540		1460	1875	2330	2785	3200
34	77	2600		1690	2100	2540	2990	3390
35	149	2830		1925	2320	2750	3180	3570
36	229	2900		2150	2530	2945	3360	3735
37	380	3080		2370	2730	3125	3520	3880
38	777	3240		2570	2910	3290	3660	4000
39	1656	3390		2750	3370	3670	3780	4100
40	3050	3460		2900	3320	3530	3870	4170
41	2725	3610		3010	3300	3610	3930	4220
42	1657	3720		3070	3350	3630	3950	4230
43	470	3690		3090	3360	3650	3940	4210
44	103	3550		3050	3315	3600	3890	4150
45	40	3530		2945	3215	3500	3790	4060
46	22	3440		2770	3050	3340	3650	3930
all weeks	11,931	3440						

TABLE 5 Median values of birth weights in the 25th—46th weeks of gestation and the percentile values calculated from them. Total series of cases.

Gestation, weeks	Number of cases	Median	Smoothed values				
		x	10 %	25 %	50 %	75 %	90 %
25	6	800	720	750	780	960	1760
26	11	975	740	820	920	1175	1935
27	12	900	740	880	1070	1400	2150
28	13	1250	765	980	1250	1630	2390
29	13	1375	855	1120	1450	1860	2550
30	26	1517	990	1280	1660	2100	2730
31	30	1720	1150	1480	1875	2340	2950
32	24	2100	1340	1690	2100	2570	3140
33	65	2617	1550	1910	2320	2800	3320
34	77	2625	1780	2140	2540	3010	3490
35	149	2846	2010	2360	2760	3210	3650
36	229	2969	2230	2580	2960	3400	3790
37	380	3132	2450	2790	3150	3570	3920
38	777	3243	2650	2980	3310	3710	4030
39	1656	3424	2830	3140	3455	3830	4120
40	3050	3530	2970	3270	3570	3920	4180
41	2725	3628	3080	3360	3650	3970	4220
42	1657	3765	3140	3410	3700	4000	4230
43	470	3718	3150	3435	3715	3980	4210
44	103	3594	3105	3345	3670	3930	4150
45	40	3600	2990	3220	3580	3830	4060
46	22	3620	2800	3030	3440	3680	3930
all weeks	11,931	3350					

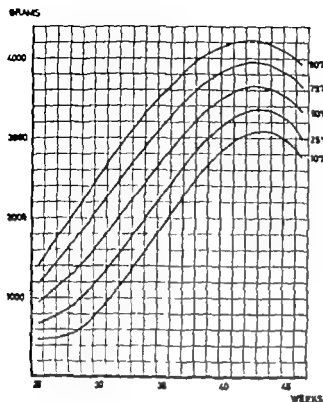


Fig 3 Intrauterine weight gain curves of the total number of cases, giving different percentiles calculated from the arithmetic mean of birth weights in the 25th—46th gestational weeks

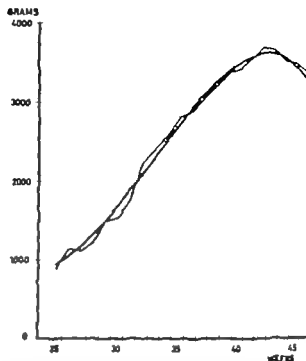


Fig 4 The 50th percentile intrauterine growth curve of the total number of cases, calculated from mean values of birth weight. One curve plotted from the unsmoothed means and another smoothed with polynomial regression of degree 3 in the 25th—46th gestational weeks

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen. The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve.

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined. The results are presented in Table 6. The table reveals that, in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 Mean values of girls and boys birth weights by weeks of gestation

Gestation weeks	Girls		Boys	
	Number	Birth weight, g	Number	Birth weight, g
25—26	9	1133	8	975
27—28	11	1136	13	1254
29—30	15	1551	24	1525
31—32	26	2088	28	1882
33—34	67	2557	75	2604
35—36	169	2813	208	2927
37—38	500	3084	657	3260
39—40	2128	3380	2558	3486
41—42	2224	3561	2148	3735
43—44	297	3577	275	3756

2 Perinatal mortality rate correlated with birth weight and gestational age

Table 28 (Appendix 3) shows the perinatal deaths cross indexed according to birth weight and gestational age in class intervals of 100 g weight and 1 week. The perinatal deaths totalled 83 159 (56.6 per cent) were boys and 122 (43.4 per cent) girls, while the sex of two was not indicated. The table also gives the perinatal mortality rates per thousand for the total number of cases by birth weight and gestational age group. Mortality rates clearly fell to a minimum in the weight range of 3500-3999 grams, and did not rise very steeply even towards the highest birth weight classes, but since the number of cases was so limited a detailed analysis was difficult. For the low birth weight infants, the first steep fall of about 50 per cent was seen in the weight range of 1800-1900 grams, and another fall of the same order in that of 2400-2500 grams that is to say the class limit separating the low birth weight group. Mortality rates per 200 gram weight groups are illustrated by the graphs of Fig. 5. In order to avoid combining the biggest birth weights group of the low birth weight infants with the 2500-2599 gram group, the weight range 600-899 was nevertheless combined. In Fig. 5 the lowest mortality rate, 3.5 per thousand, was in the 3500-3699 gram range, but if the groups had been differently combined the mortality rate would be equally low in the 3800-3999 gram range.

Table 8 also shows that mortality rates calculated according to the gestational week are at their lowest in the 40th week of gestation. Pre-term births exhibit a roughly 50 per cent fall in mortality from the 31st to the 32nd week and again from the 36th to the 37th week. Fig. 6 presents mortality rates according to gestational age by fortnightly periods. The pre-term group limit of the beginning of the 38th week does not coincide with a steep fall, whereas mortality increases

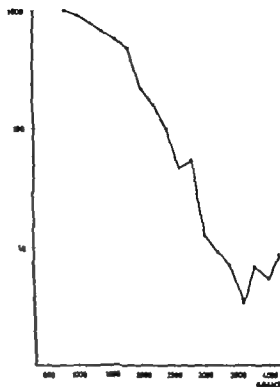


Fig. 5. Perinatal mortality by 200 gram birth weight groups.



Fig. 6. Perinatal mortality by week of gestation. The rates are calculated for fortnightly period.

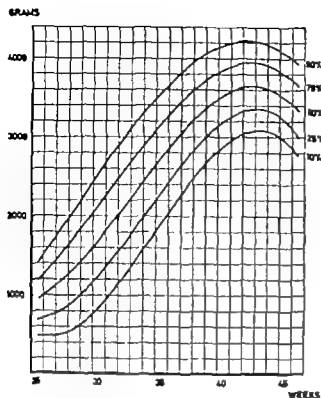


Fig 3 Intrauterine weight gain curves of the total number of cases growing different percentiles calculated from the arithmetic mean of birth weights in the 25th-46th gestational weeks.

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen. The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve.

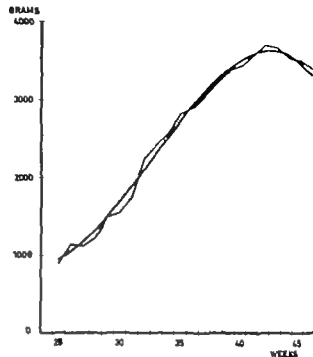


Fig 4 The 50th percentile intrauterine growth curve of the total number of cases, calculated from mean values of birth weight. One curve plotted from the unsmoothed means and another smoothed with polynomial regression of degree 3 in the 25th-46th gestational weeks.

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined. The results are presented in Table 6. The table reveals that, in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 Mean values of girls' and boys' birth weights by weeks of gestation

Gestation, weeks	Girls		Boys	
	Number	Birth weight, g	Number	Birth weight, g
25-26	9	1133	8	975
27-28	11	1136	13	1254
29-30	15	1553	24	1525
31-32	26	2088	28	1882
33-34	67	2537	75	2604
35-36	169	2813	208	2927
37-38	500	3084	657	3260
39-40	2128	3380	2558	3486
41-42	2224	3561	2148	3733
43-44	297	3577	275	3756

2. Perinatal mortality rate correlated with birth weight and gestational age

Table 28 (Appendix 3) shows the perinatal deaths cross-indexed according to birth weight and gestational age in class intervals of 100 g weight and 1 week. The perinatal deaths totalled 283 159 (56.6 per cent) were boys and 122 (43.4 per cent) girls, while the sex of two was not indicated. The table also gives the perinatal mortality rates per thousand for the total number of cases by birth weight and gestational age group. Mortality rates clearly fell to a minimum in the weight range of 3500-3999 grams, and did not rise very steeply even towards the highest birth weight classes, but since the number of cases was so limited a detailed analysis was difficult. For the low birth weight infants, the first steep fall of about 50 per cent was seen in the weight range of 1800-1900 grams, and another fall of the same order in that of 2400-2500 grams, that is to say the class limit separating the low birth weight group. Mortality rates per 200 gram weight groups are illustrated by the graphs of Fig. 5. In order to avoid combining the biggest birth weight group of the low birth weight infants with the 2500-2999 gram group, the weight range 600-899 was nevertheless combined. In Fig. 5 the lowest mortality rate, 3.5 per thousand, was in the 3500-3699 gram range, but if the groups had been differently combined the mortality rate would be equally low in the 3800-3999 gram range.

Table 28 also shows that mortality rates calculated according to the gestational week are at their lowest in the 40th week of gestation. Pre-term births exhibit a roughly 50 per cent fall in mortality from the 31st to the 32nd week and again from the 36th to the 37th week. Fig. 6 presents mortality rates according to gestational age by fortnightly periods. The pre-term group limit of the beginning of the 38th week does not coincide with a steep fall, whereas mortality increases

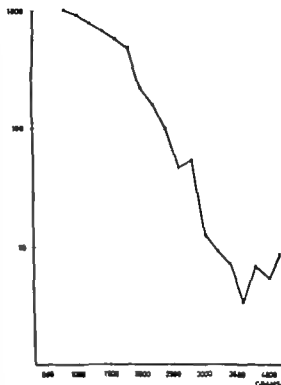


Fig. 5. Perinatal mortality by 200 gram birth weight groups.

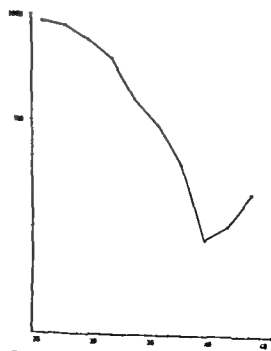


Fig. 6. Perinatal mortality by week of gestation. The rates are calculated for fortnightly periods.

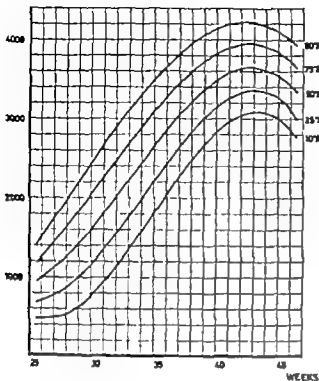


Fig 3 Intrauterine weight gain curves of the total number of cases, giving different percentiles calculated from the arithmetic mean of birth weights in the 25th—46th gestational weeks.

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen. The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve.

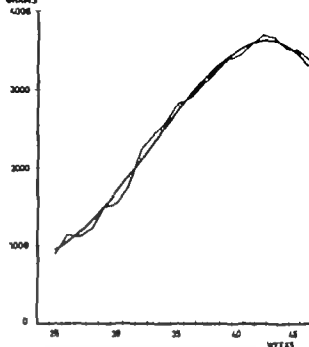


Fig 4 The 50th percentile intrauterine growth curve of the total number of cases calculated from mean values of birth weight. One curve plotted from the unsmoothed means and another smoothed with polynomial regression of degree 3 in the 25th—46th gestational weeks.

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined. The results are presented in Table 6. The table reveals that in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 Mean values of girls' and boys' birth weights by weeks of gestation

Gestation, week	Girls		Boys	
	Number	Birth weight, g	Number	Birth weight, g
25—26	9	1133	8	1275
27—28	11	1136	13	1254
29—30	15	1553	24	1525
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33—34	67	2537	75	2604
35—36	169	2813	208	2927
37—38	500	3084	657	3260
39—40	2128	3380	2558	3486
41—42	2224	3561	2148	3735
43—44	297	3577	275	3756

TABLE 9 Comparison of the birth weights of infants of different gestational ages by groups. 1 those who died before the beginning of delivery 2 those who died during delivery or the neonatal period and 3 those who were living at the end of the perinatal period. The differences of the means of the birth weights were tested by Student's *t* test ($^{**}P<0.05$, $^{***}P<0.01$)

Gestational weeks	1 Deaths before beginning of delivery		2 Deaths during delivery and neonatal period		3 Survivals at the end of perinatal period		<i>t</i> calculated for differences of mean birth weights of Groups 1 and 2	calculated for differences of mean birth weights of Groups 2 and 3
	Number of cases	Mean birth weight g	Number of cases	Mean birth weight g	Number of cases	Mean birth weight g		
25-26	2	1,500	12	875	3	1,300	—	2.90
27-29	10	989	16	1,143	12	1,733	0.72	2.65
30-3	12	1,325	24	1,462	44	2,188	0.97	4.54
33-35	18	1,683	18	2,177	255	2,812	2.31	4.25
36-38	31	2,196	29	2,635	1,326	3,169	2.23	4.98
39-41	21	2,844	41	3,014	7,369	3,502	0.81	6.97 ^{**}
42-44	10	3,339	20	3,259	2,200	3,709	0.35	3.46
More than 44 weeks, or unknown	10	1,659	9	1,933	459	3,304	0.59	8.04
Total	114	2,085	169	2,185	11,648	3,474	1.64	22.97 ^{***}

cases and separately for 8 gestational age groups. The results are presented in Table 9.

A comparison of the mean birth weights of group 1 with those of group 2 revealed that the weights of the former in the 33rd to 38th week of gestation were statistically significantly lower. In the other weeks of gestation the difference was not significant. When the birth weights of group 2 were compared with those of group 3 the birth weights of the surviving infants were found to be higher and the differences to be markedly larger than in the former comparison. They were statistically significant for every week of gestation. Summarizing, it may be said that the birth weights of infants who died during the perinatal period were significantly lower than those of infants of the same gestational age who survived and that the birth weights of infants who died before the beginning of labour were slightly lower than those of the infants who died later during the perinatal period.

Fig. 7 presents a graph of the 50th percentile of the intrauterine growth curve, with values

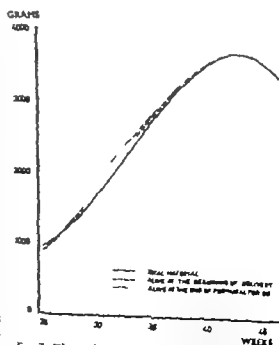


Fig. 7 The 50th percentile values of the intrauterine growth curve calculated on the total number of cases, on the infants alive at the beginning of delivery and on those alive at the end of the perinatal period.

TABLE 7 *Distribution of the cases into zones limited by the percentiles of intrauterine growth curves Pre term term and post term infants and their relevant perinatal mortality rates are listed separately*

Gestation weeks	Over 90 percentiles			50—90 percentiles			10—50 percentiles			Under 10 percentiles			Total		
	No. of infants	Total	Mortality rate per thousand	No. of infants	Total	Mortality rate per thousand	No. of infants	Total	Mortality rate per thousand	No. of infants	Total	Mortality rate per thousand	No. of infants	Total	Mortality rate per thousand
37 weeks or less	6	104	57.7	17	369	46.1	83	466	178.1	42	96	437.5	148	1,035	143.0
38—42 weeks	4	794	5.0	20	3,820	5.2	31	4,411	7.0	49	840	58.3	104	9,865	10.6
43 weeks or more	1	83	12.0	3	244	12.3	3	241	12.4	6	68	88.2	13	636	20.5
Total	11	981	11.2	40	4,433	9.0	117	5,118	12.9	97	1,004	96.6	265	11,536	23.0

by roughly 100 per cent at the post term class limit of the end of the 42nd week

Table 7 presents the mortality by gestational age and the various percentiles of the intrauterine growth curve. An analysis of the overall results of this classification revealed that the mortality rate was lowest between the 50th and 90th percentiles. In the over 90 percentile range the mortality rate was slightly higher but the difference was not statistically significant and was only present in pre-term infants. From the 10th to 50th percentile the mortality rate was more than twice that of over 50. Under the 10th percentile the rate was more than four times that of the 50—10 percentile range. According to gestational age the mortality rate for pre-term infants was about 14 times that of term births while the rate for post term infants was twice that of the term births.

The majority of the cases in the early gestational weeks were perinatal deaths moreover 160 of the 283 deaths were still births (Table 1). For this reason the birth weights of the infants who died at different phases of the perinatal period were compared with those of the survivors. Table 8 analyses the 160 stillbirths according to whether death

occurred before birth or during delivery separately for the low birth weight infants and those with birth weights of 2500 g or more.

TABLE 8 *Stillbirths classified into deaths before the beginning of delivery and those during delivery*

Birth weight	≥ 2500 g	<2500 g	Total	Per cent
Deaths before beginning of delivery	35	68	103	64.4
Deaths during delivery	29	17	46	28.7
Time of death unknown	6	5	11	6.9
Total	70	90	160	100.0

The birth weights of the following groups were compared. Group 1 deaths before the beginning of delivery (11 stillbirths of unknown time of death were included in this group). Group 2 deaths during delivery or the neonatal period, and Group 3 survivals at the end of the perinatal period. This classification was imposed on the total number of

TABLE 10. Eigenvectors of discriminant function analyses A A1 B B1 and C Weightings of the variables have been scaled and normalized A + sign on the top of a vector indicates that positive values of weightings of variables of this vector are associated with the risk group - sign indicates that negative values of the weightings are associated with the risk group

	A +	A1 -	B -	B1 +	C -
1 Maternal age	-0.30701	0.28471	0.18095	-0.24452	0.53295
2 Maternal height	-0.13111	0.12539	0.09841	-0.11054	0.29192
3 Maternal weight	-0.29079	0.34209	-0.01458	-0.04623	-0.08103
4 Menstrual age	-0.06048	0.07505	0.00682	-0.03301	0.08721
5 Parity	-0.11849	0.41418	-0.14531	-0.33161	0.22475
6 Number of previous abortions	0.13198	-0.18172	-0.18746	0.28420	0.02541
7 Previous low birth weight infants	0.54215	-0.58377	-0.36805	0.50229	-0.02436
8 Previous perinatal mortality	0.00991	-0.06371	-0.02300	0.12671	0.02359
9 Mother's marital status	0.28481	-0.33745	-0.19687	0.26361	0.05336
10 Mother occupation	0.12150	0.11143	-0.10814	-0.12531	0.01668
11 Father's occupation	0.07727	-0.13992	-0.03998	0.07613	-0.10335
12 Is the father farmer	0.05262	0.06373	0.15182	-0.13532	-0.00031
13 Mother sector of economy	0.08473	-	-0.08306	-	-0.14489
14 Father sector of economy	-0.10100	-	0.11872	-	-0.11108
15 Mother vocational standing	-0.04488	-0.12547	-0.10638	0.23257	0.02211
16 Father vocational standing	-	0.02525	-	-0.02341	-
17 Occupation of mother father	0.03670	-	-0.10266	-	0.07279
18 Was mother father farmer	-0.03541	-	0.05089	-	0.11866
19 Number of mother siblings	-0.06419	-	-0.06302	-	0.22745
20 Number of mother deceased siblings	0.03518	-0.03684	-0.09103	0.11038	-0.16221
21 Mother school attendance	-0.01418	0.05838	0.06397	-0.12498	0.17217
22 Intellectual interest in house-keeping and public health facilities	0.00453	-0.15381	-0.07437	0.22276	0.03307
23 Was the pregnancy wanted or not	-	-0.06685	-	-0.01100	-
24 Mother frame of mind during pregnancy	0.08396	-0.01370	-0.06293	0.05093	0.04839
25 Mother's attitude towards support by public authorities	-	0.02679	-	0.03491	-
26 Mother smoking	0.20727	-0.02265	-0.12121	-0.03394	0.14322
27 Mother attitude to strenuousness of work	-	-	-	-	-
28 Mother gainful employment	-0.02363	-0.01734	0.02219	0.06952	0.13145
29 Presence at work	-0.04325	-	0.09389	-	0.17091
30 Does the mother work outdoors or indoors	0.03570	-	-0.16124	-	0.03300
31 Housekeeping help	0.03936	-	0.06779	-	-0.07200
32 Number of persons in the household	-0.03193	-	0.09396	-	0.17250
33 Number of children under 15 years of age	-0.32570	-	0.47893	-	-0.01840
34 Number of rooms	0.07388	0.08757	0.12387	-0.21732	-0.02210
35 Electricity in the house	-0.07143	-	-0.01352	-	0.01840
36 Running water in the house	-0.01240	-	0.14740	-	0.08200
37 Has the family house of its own	0.06568	-	0.00612	-	-0.06300
38 Ownership of TV set	0.03591	-	0.11038	-	0.02600
39 Ownership of car	0.12586	-	-0.07081	-	-0.22500
40 Degree of industrialization of the place of residence	-0.07590	0.09324	0.12938	-0.20321	0.31700
41 Character of the place of residence urban or rural	0.00452	-	-0.11829	-	-0.11200
42 Internal migration	0.13728	0.06256	0.21094	-0.24046	0.14300
43 Character of earlier place of residence	0.10813	0.07019	0.15516	-0.20329	-0.00000
44 Distance to antenatal clinic	-0.07337	-	-0.03433	-	0.04000
45 Distance to neighbour	-0.03440	-	-0.01747	-	-0.03000
46 Distance to centre of population	-0.15701	0.06319	0.31743	-0.16138	0.24000
47 Distance to medical officer	0.29040	-	-0.26379	-	-0.14000

calculated 1 on the total number of cases, 2. on the cases excluding intrauterine deaths, and 3 on the cases excluding all perinatal deaths. Differences in the growth curves are only apparent before the 37th week of gestation the relative number of later deaths being small. The retardation of the curve in babies dying in utero alone seems to be of no practical importance, whereas the differing course of the curve plotted according to survivals alone is of practical significance before the 34th week of gestation.

3 Perinatal mortality rate and birth weight correlated to maternal biological characteristics and socio-economic circumstances and prediction of the former from the latter

a. Discriminant function analyses

The eigenvectors, i.e. discriminants, of analyses A, A1, B, B1 and C (see page 14) are presented in Table 10. The weighting of the variables is indicated as scaled and normalized so that the range of the weightings is from -1 to +1 and the sums of the squares of the weightings of each eigenvector is 1. The significance of the eigenvectors was tested with Rao's chi square approximation and the results are given below.

Analysis	Number of variables	Eigen-vector	Chi square	Degrees of freedom	P
A	43	0.1896	56.3	43	< 0.001
A1	27	0.1369	216.3	27	< 0.001
B	43	0.1508	160.3	43	< 0.001
B1	27	0.1115	121.5	27	< 0.001
C	43	0.0655	69.6	43	< 0.01

The group means and group standard deviation in each analysis were as follows:

Analysis	Controls		Risk group	
	Mean	Standard deviation	Mean	Standard deviation
A	-1.871	0.530	-1.323	0.714
A1	3.609	0.496	3.120	0.727
B	2.804	0.561	2.143	0.761
B1	-3.422	0.547	-2.864	0.750
C	10.681	0.785	10.026	0.825

The group means on the discriminants were relatively close to one another and group dispersions were to some extent overlapping.

From the consideration of the group means the effect of the + or - sign of the weightings of the eigenvector can be seen. The + sign indicates that high values of this variable are associated with the group with the higher mean and the - sign indicates that high values of this variable are associated with the group with the lower mean.

In the different analyses the signs associated with membership of the different risk groups were A + A1 - B - B1 + C -. In Table 10 the sign discriminating cases towards the risk group is given in front of each vector. The higher the weighting of the variable the more important is the variable. Appendix 1 shows how each variable has been recorded. For example, age is given in terms of the year of birth and since in the analyses an increasing score is associated with the control group, low age is a characteristic of the control group while advancing age is associated with the risk group.

The percentage distribution of the control and risk group cases on the basis of the classification procedure of discriminant function analyses A and C into different probability levels is presented in Fig. 8. Probability in this context means that, if a case e.g. has over 90 per cent probability of belonging to the low birth weight group, the discriminant score of the case is close to the point of maximum density of this group in discriminant space. The empirical risk for such a case of giving birth to a low birth weight infant will be described further below (p. 26).

TABLE 10 Eigenvectors of discriminant function analyses A A1 B B1 and C Weightings of the variables have been scaled and normalized. A + sign on the top of a vector indicates that positive values of weightings of variables of this vector are associated with the risk group a - sign indicates that negative values of the weightings are associated with the risk group

	A +	A1 -	B -	B1 +	C -
1 Maternal age	-0.30701	0.28671	0.18095	-0.24452	0.53295
2 Maternal height	-0.13111	0.12539	0.09841	-0.11054	0.29192
3 Maternal weight	-0.29079	0.34209	-0.01458	-0.04623	-0.08103
4 Menarche age	-0.06048	0.07505	0.00682	-0.03301	0.08721
5 Parity	-0.11349	0.41418	-0.14331	-0.33161	0.22473
6 Number of previous abortions	0.13198	-0.18172	-0.18746	0.28420	0.02341
7 Previous low birth weight infants	0.56215	-0.58377	-0.36805	0.30229	-0.02436
8 Previous perinatal mortality	0.00991	-0.06371	-0.02300	0.12671	0.02359
9 Mother marital status	0.28481	-0.33745	-0.19687	0.26361	0.05336
10 Mother occupation	0.12150	0.11143	-0.10814	-0.12331	0.01668
11 Father's occupation	0.07727	-0.13932	-0.03998	0.07613	-0.10335
12 Is the father farmer	0.05262	0.06373	0.15182	-0.13532	-0.00031
13 Mother sector of economy	0.08473	-	-0.08506	-	-0.14689
14 Father sector of economy	-0.10100	-	0.11872	-	-0.11108
15 Mother' occupational standing	-0.04488	-0.12547	-0.10638	0.23207	0.02211
16 Father vocational standing	-	0.02523	-	-0.02341	-
17 Occupation of mother father	0.03670	-	-0.10266	-	0.07279
18 Was mother' father farmer	-0.03561	-	0.05089	-	0.11866
19 Number of mother siblings	-0.06419	-	-0.06302	-	0.22745
20 Number of mother' deceased siblings	0.03318	-0.03684	-0.09103	0.11038	-0.16221
21 Mother school attendance	-0.01418	0.05838	0.06997	-0.12498	0.17217
22 Intellectual interest in house keeping and public health facilities	0.00453	-0.15381	-0.07437	0.22276	0.03307
23 Was the pregnancy wanted or not	-	-0.06685	-	-0.01100	-
24 Mother frame of mind during pregnancy	0.08396	-0.01370	-0.06293	0.05093	0.04839
25 Mother's attitude towards support by public authorities	-	0.02679	-	0.03491	-
26 Mother' smoking	0.20727	-	-0.12121	-	0.14322
27 Mother attitude to strenuousness of work	-	-0.02363	-	-0.03394	-
28 Mother grateful employment	-0.02363	-0.01734	0.02219	0.06952	0.13145
29 Poverty at work	-0.04323	-	0.09389	-	0.17098
30 Does the mother work outdoors or indoors	0.03570	-	-0.16126	-	0.03308
31 Housekeeping help	0.03936	-	0.06729	-	-0.07207
32 Number of persons in the household	-0.03193	-	0.09396	-	0.17256
33 Number of children under 15 year of age	-0.32570	-	0.67893	-	-0.01848
34 Number of rooms	0.02388	0.08737	0.12387	-0.1732	-0.02284
35 Electricity in the house	-0.07143	-	-0.01352	-	0.01847
36 Running water in the house	-0.01240	-	0.14740	-	0.08283
37 Has the family house of its own	0.06368	-	0.00612	-	-0.06382
38 Ownership of TV set	0.03591	-	0.11038	-	0.02698
39 Ownership of car	0.12386	-	-0.07081	-	-0.22567
40 Degree of industrialization of the place of residence	-0.07590	0.09324	0.12938	-0.20321	0.31705
41 Character of the place of residence urban or rural	0.00452	-	-0.11829	-	-0.11230
42 Internal migration	0.13728	0.06236	0.21094	-0.24046	0.14332
43 Character of earlier place of residence	0.14813	0.07019	0.15316	-0.20529	-0.00049
44 Distance to antenatal clinic	-0.07337	-	-0.03433	-	0.04145
45 Distance to neighbour	-0.03440	-	-0.03747	-	-0.20302
46 Distance to centre of population	-0.15701	0.06319	0.31743	-0.16138	0.24615
47 Distance to medical officer	0.29040	-	-0.26379	-	-0.14649

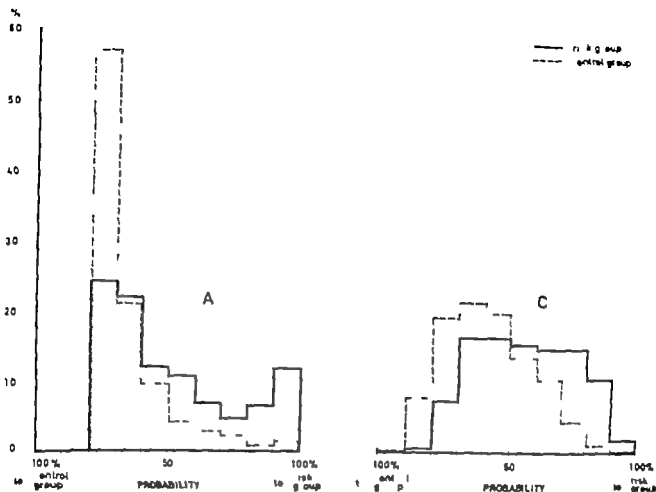


Fig 8 Percent age distribution of the control and risk group cases on the basis of the probability classification by discriminant function analyses A and C

A at the analysis in which the two groups are controls and two birth weight infants

C the analysis in which the two groups are controls and perinatal death b birth weight of 1000 g or more

As suggested by Rao's significance test the discriminating power of analysis C is less than that of analysis A. This is also evident from Fig 8. The probability distributions of analysis A show distinct clusterings where the probability of right group membership is relatively high whereas in the probability distribution of analysis C the peak of the percentage clustering for both groups is close to the 50 per cent probability point.

Table 11 shows the number of cases of analysed groups with over 50 per cent probability of risk group membership according to the different analyses. In a study like the present where the total distribution was very uneven or in other words the proportion of risk group in the total series was small

TABLE 11 Probability distribution of cases in groups of discriminant function analyses towards risk groups in each analysis

Analyses and their groups		Over 50 per cent probability of risk group membership	
		Number of cases	Per cent of total group
A	Control group	122	12.20
	Risk group	706	41.28
A 1	Control group	98	9.80
	Risk group	167	33.47
B	Control group	110	11.00
	Risk group	69	42.07
B 1	Control group	115	11.50
	Risk group	59	35.98
C	Control group	303	30.30
	Risk group	69	57.98

it is essential for the identification of risk group cases that the percentage of cases falsely included in the risk group is low compared with the total number of cases. This may be considered to be the case at 50 per cent probability level in analyses A, A 1 B and III 1 that is to say in all analyses concerned with the low birth weight babies, since the percentage of falsely classified control group cases was 9.8–12.2 per cent. By contrast, in analysis C which concerns infants with a minimum birth weight of 2500 g, 30.3 per cent of the controls were included in the risk group at the 50 per cent probability level.

b Result of probability classification of total series on the basis of the discriminant function analysis concerned with low birth weight infants

The cases not involved in the analysis itself were also classified by the analysis A classification programme. These three groups are listed below together with the percentage of cases with over 50 per cent probability of risk group membership.

Classified group	Total cases in the group	Over 50 per cent probability of risk group membership	
		Number of cases	Per cent of total group
Birth weight \geq 2000 g, deaths	119	82	18.49
Birth weight \geq 2500 g perinatal age \leq 37 weeks, survivors	696	133	19.11
Birth weight \geq 2500 g, perinatal age \geq 43 weeks, survivors	617	71	11.53

Table 12 shows the probability based on classification of all cases by analysis A, of risk group membership at 10 per cent inter-

vals. Table 13 gives, separately the probability classification of all perinatal deaths, with mortality rates, while Table 14 presents the relevant low birth weight rates. A study of the results concerned with mortality rates and low birth weight rates yields four groups: probability ranges 20–30 per cent, 30–50 per cent, 50–80 per cent, and over 80 per cent, the percentages indicating the degree of probability of risk group membership. The probabilities obtained for all cases combined by this method are shown in Table 15 both for the total number of cases, mortality rates and low birth weight rates. The empirical risk of mothers in the probability ranges determined by the discrimination scores giving birth to a child of low birth weight can now be established: in the range 20–30 per cent it is 1.9 per cent, 30–50 per cent 4.6 per cent, 50–80 per cent 9.2 per cent, and 80–100 per cent 22.0 per cent (Table 15).

The cases were thus divided into the following four groups.

Low risk groups

- 1 20–30 per cent probability of membership of the low birth weight group. This group comprised just over half the total number of cases. The low birth weight rate was less than half the rate of the initial series. The mortality rate was 30 per cent lower than that of the initial series.
- 2 30–50 per cent probability of membership of the low birth weight group. One-third of the total number of cases belonged to this group. Both the low birth weight rate and mortality rate were slightly higher than, yet of the same order of magnitude as, in the initial series.

High risk groups

- 3 50–80 per cent probability of membership of the low birth weight group. This group comprised one-tenth of the total number of cases. The low birth weight rate was

TABLE 12 *Distribution of all cases on the basis of the probability classification by analysis A. The result is indicated as the probability of risk group membership*

Birth weight groups	Probabilities of membership of group with birth weight under 2500 g. per cent.										Total
	0-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100		
under 2500 g. all	0	122	110	61	53	35	24	34	60	499	
2500 g. or more, perinatal deaths	0	55	30	12	10	6	3	1	2	119	
2500 g. or more, gestation 38-42 weeks, survivals	0	3,700	2,100	980	440	290	230	100	160	10,000	
2500 g. or more, gestation 37 weeks or less, survivals	0	350	153	60	44	27	13	24	25	696	
2500 g. or more, gestation 43 weeks or more, survivals	0	333	156	57	22	14	13	15	7	617	
Total	0	6,560	2,549	1 170	569	372	283	174	254	11 931	

TABLE 13 *Distribution of perinatal deaths by probability classification of analysis A and mortality rates per thousand by degrees of probability. The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g. per cent.								Total
	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	
Deaths	106	61	31	30	14	10	11	70	43
Total number of the group	6,560	2,549	1,170	569	372	283	174	254	11,931
Mortality rate per thousand	16.2	23.9	26.5	52.7	37.6	35.3	63.2	79.7	23.7

TABLE 14 *Distribution of low birth weight infants by probability classification of analysis A and percentages of the low birth weight infants by degrees of probability. The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g. per cent.								Total
	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	
Number of low birth weight infants	122	110	61	53	35	24	34	60	499
Total number of the group	6,560	2,549	1,170	569	372	283	174	254	11,931
Low birth weight rate per cent	1.9	4.3	5.2	9.3	9.4	8.5	19.5	23.6	4.2

TABLE 15 *Distribution of the total number of cases using four probability ranges by probability classification of analysis A mortality rates and low birth weight rates*

	Probabilities of membership of group with birth weight under 2500 g. per cent.					Total
	20-30	30-50	50-80	80-100		
Total number of the group	6,560	3,719	1,224	428		11,931
Low birth weight rate per cent	1.9	4.6	9.2	22.0		4.2
Mortality rate, per thousand	16.2	24.7	44.1	72.4		23.7

TABLE 16. Means and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1-4 formed on the basis of the probability levels obtained from discriminant function analysis A.

	Low risk groups		High risk groups		Total cases
	1	2	3	4	
Mean birth weight, g	3544±326	3408±353	3183±596	2974±744	3444±569
Mean length at birth, cm	50.6±2.3	50.1±2.3	49.3±2.9	48.1±3.2	50.2±2.5

more than twice, and the mortality rate nearly twice that of the initial series.

- 4 over 80 per cent probability of membership of the low birth weight group. The group comprised some 3.5 per cent of the total number of cases. The low birth weight rate was five times and the mortality rate more than three times that of the initial series.

This classification into low risk and high risk groups will be used in the following.

Table 16 presents the mean values and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1-4. The differences from one group to the other are evident, the birth weight and length at birth diminishing as the probability of risk increases.

False classification may be assumed in all those cases from the high risk groups in which the child survived and had a minimum birth weight of 2500 g. For this reason, the mean birth weights of these children were calculated separately and in groups 1-4 were 3577, 3495, 3321 and 3292 g, respectively. Since the low risk group 1 comprises more than half the total number of cases, the infants with the lowest probability of risk group membership, under the 22.5 per cent probability level, were examined separately. These cases numbered 1011; their mean birth weight was 3771 ± 472 g and mean length at birth 51.4 ± 1.8 cm. Since the birth weights of the falsely classified were markedly lower than those of

the correctly classified, one may ask whether the classification really was false and take it that the infants of a minimum birth weight of 2500 g and living beyond the perinatal period very largely represented the biological variation inside the high risk group.

Survival might also be measured as a continuous variable which would indicate the different degrees of health. It could not be used for the present purpose, and in analysis A, the group consisting of all low birth weight infants, the increased mortality rate of the high risk group may be considered as associated with their low birth weight. The following calculation was made to prove this. The mortality in the total number of cases per each 500 gram weight range was calculated (Tables 27 and 28 in Appendices 2 and 3), and according to this mean the number of deaths which risk groups 3 and 4 ought to show on the basis of their combined weight distribution was estimated. The number of deaths predicted in this way was 93 while the true number was 85. The difference in the numbers is not statistically significant, and therefore the increased mortality of the risk group of analysis A can be assumed to be associated with low birth weight.

For a more detailed study of the characteristics of risk group infants, the low and high risk groups 1-2 and 3-4 were combined since the number of cases in the latter groups was small. They displayed the following characteristics.

TABLE 12 *Distribution of all cases on the basis of the probability classification by analysis A. The result is indicated as the probability of risk group membership*

Birth weight groups	Probabilities of membership of group with birth weight under 2500 g. per cent.									Total
	0-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	
under 2500 g. all	0	122	110	61	53	35	24	34	60	499
2500 g. or more perinatal deaths	0	55	30	12	10	6	3	1	2	119
2500 g. or more gestation 38-42 weeks, survivals	0	5,700	2,100	980	440	290	230	100	160	10,000
2500 g. or more, gestation 37 weeks or less, survivals	0	330	153	60	44	27	13	24	25	696
2500 g. or more gestation 43 weeks or more survivals	0	333	156	57	24	14	13	15	7	617
Total	0	6,560	2,549	1,170	569	372	283	174	254	11,931

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	Probabilities of membership of group with birth weight under 2500 g. per cent.									Total
	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100		
Deaths	106	61	31	30	14	10	11	20	243	
Total number of the group	6,560	2,549	1,170	569	372	283	174	254	11,931	
Mortality rate per thousand	16.2	23.9	26.5	52.7	37.6	35.3	63.2	78.7	23.7	

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	Probabilities of membership of group with birth weight under 2500 g. per cent.									Total
	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100		
Number of low birth weight infants	122	110	61	53	35	4	34	60	499	
Total number of the group	6,560	2,549	1,170	569	372	283	174	254	11,931	
Low birth weight rate per cent	1.9	4.3	5.2	9.3	9.4	8.5	19.5	23.6	4.2	

TABLE 15 *Distribution of the total number of cases using four probability ranges by probability classification of analysis A mortality rates and low birth weight rates*

	Probabilities of membership of group with birth weight under 2500 g. per cent.				Total
	20-30	30-50	50-80	80-100	
Total number of the group	6,560	3,719	1,224	428	11,931
Low birth weight rate, per cent	1.9	4.6	9.2	22.0	4.2
Mortality rate per thousand	16.2	24.7	44.1	72.4	23.7

TABLE 16. Means and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1-4 formed on the basis of the probability levels obtained from discriminant function analysis A

	Low risk groups		High risk groups		Total cases
	1	2	3	4	
Mean birth weight, g	3544 \pm 526	3406 \pm 533	3183 \pm 596	2974 \pm 744	3444 \pm 569
Mean length at birth, cm	50.6 \pm 2.3	50.1 \pm 2.5	49.3 \pm 2.9	48.1 \pm 3.8	50.2 \pm 2.5

more than twice, and the mortality rate nearly twice that of the initial series.

- 4 over 80 per cent probability of membership of the low birth weight group. The group comprised some 3.5 per cent of the total number of cases. The low birth weight rate was five times and the mortality rate more than three times that of the initial series.

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For a more detailed study of the characteristics of risk group infants, the low and high risk groups 1-2 and 3-4 were combined since the number of cases in the latter groups was small. They displayed the following characteristics.

	Low risk group	High risk group
Number of cases	10,279	1,652
Boys/1000 girls	1111	910
Mean birth weight, g	3495±540	3129±644
Mean length at birth, cm	50.4±1.3	49.0±1.2
Mean gestational age, days	278±14.0	272.7±19.2
Low birth weight rate, per cent	2.8	12.5
Perinatal mortality rate, per 1000	19.3	51.4

If the high risk group is studied by 100 gram weight groups, the majority of cases was in group 3100-3199 g 10.2 per cent while the weight range of 3100-3399 g covered 26.2 per cent. In the low risk group the majority of cases, 9.0 per cent was in the 3500-3599

g group while weight range 3500-3799 g covered 26.3 per cent

Table 17 shows the percentage composition of the 500 gram weight classes in high and low risk groups, and Table 18 presents the distribution of gestational weeks in these groups. The result was more conclusive for birth weight over 50 per cent of the lowest weight group was composed of the high risk group and the share decreased regularly on transition to the higher weight groups so that birth weights exceeding 4500 g equalled only about 3 per cent of the high risk group. The study of gestational age gave a parallel result

TABLE 17 *Distribution of cases from the different weight groups into high risk and low risk groups on the basis of the probability classification by discriminant function analysis A*

Weight groups g	High risk group		Low risk group		Total	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
less than 1500	49	51.6	46	48.4	95	100.0
1500-1999	40	40.0	60	60.0	100	100.0
2000-2499	117	38.5	187	61.5	304	100.0
2500-2999	292	22.3	1,018	77.7	1,310	100.0
3000-3499	642	16.6	3,225	83.4	3,867	100.0
3500-3999	401	9.1	4,013	90.9	4,414	100.0
4000-4499	99	6.8	1,351	93.2	1,450	100.0
4500-4999	10	3.1	314	96.9	324	100.0
5000 and more	2	3.0	65	97.0	67	100.0
Total	1,652	13.8	10,279	86.2	11,931	100.0

TABLE 18 *Distribution of cases from the different gestational age groups into high risk and low risk groups on the basis of the probability classification by discriminant function analysis A*

Week of gestation	High risk group		Low risk group		Total	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
25-26	6	35.3	11	64.7	17	100.0
27-29	16	42.1	22	57.9	38	100.0
30-32	31	38.7	49	61.3	80	100.0
33-35	77	26.5	214	73.5	291	100.0
36-38	237	17.1	1,149	82.9	1,386	100.0
39-41	997	13.4	6,434	86.6	7,431	100.0
42-44	233	10.4	1,997	89.6	2,230	100.0
45 or more	9	14.3	54	85.7	63	100.0
Total	1,606	13.9	9,930	86.1	11,536	100.0

TABLE 19 Location of the high risk and low risk group cases by the probability classification of discriminant function analysis A of all low birth weight infants in the zones determined by the percentiles of the intrauterine growth curve of the total number of cases

	Location of the cases on the intrauterine growth curve							
	Below 10th percentile		Between 10th and 50th percentiles		Between 50th and 90th percentiles		Above 90th percentile	
	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone
High risk group	270	26.9	842	16.4	462	10.4	32	3.3
Low risk group	732	73.1	4,278	83.6	3,971	89.6	949	96.7
Total	1,002	100.0	5,120	100.0	4,433	100.0	981	100.0

TABLE 20 Mean birth weights of the high risk and low risk group cases at given gestational ages on the basis of the probability classification by discriminant function analysis A of all low birth weight infants and : for the significance of the difference in mean birth weights ($^*P < 0.10$ $P < 0.05$ $P < 0.01$)

Week of gestation	High risk group		Low risk group		for difference in mean birth weights
	Number of cases	Mean birth weight, g	Number of cases	Mean birth weight, g	
25-26	6	1,017	11	1,082	0.58
27-28	11	1,282	14	1,093	2.12
29-30	16	1,450	23	1,596	1.89*
31-32	20	1,835	34	2,068	2.96
33-34	44	2,309	98	2,491	7.83
35-36	85	2,656	293	2,938	9.47*
37-38	183	2,936	972	3,231	15.56
39-40	725	3,255	3,972	3,470	25.31
41-42	438	3,396	3,444	3,676	25.72
43-44	67	3,330	506	3,709	12.82
Over 44 or not known	55	2,676	403	3,318	19.31
Total	1,652	3,129	10,279	3,495	58.64

though the decrease was less abrupt. Before the 33rd week of gestation, the high risk group comprised 35-42 per cent and from the 39th week onwards 10-14 per cent of the gestational age groups.

Table 19 specifies the high and low risk groups in the percentile zones of the intrauterine growth curve. If the location of high risk cases is reviewed by number it is found that nearly 9 times as many cases are located

below the 10th percentile as above the 90th percentile, while nearly twice as many cases are located between the 10th and 50th as between the 50th and 90th percentiles. 26.9 per cent of all cases located below the 10th and 3.3 per cent of those located above the 90th percentile belonged to the high risk group.

Table 20 gives the mean birth weights of the high and low risk cases when the groups

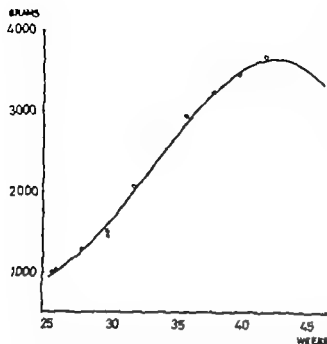


Fig 9 The 50th percentile intrauterine growth curve of the total number of cases and the mean birth weights by week of gestation in the groups obtained from probability classification by discriminant function analysis A which concerned all low birth weight infants.

● high risk group
○ low risk group

are divided into fortnightly periods by gestational age. From the 29th to 30th gestational week onwards the birth weights of the high risk group were lower and the difference was statistically highly significant from the 31st to 32nd week onwards. The findings are plotted in the graph of Fig 9.

The high risk group contained relatively fewer boys per 1000 girls than the initial series, in the former 910 and in the latter 1086. The difference was statistically highly significant.

c. Variables used in discriminant function analysis

The greater the weighting of a variable on the eigenvector, the greater part that variable plays in the discriminant function. There is, however, no specific test to indicate the significance of the weighting.

The 15 variables with the highest weighting in discriminant function analysis A are listed

below biological characteristics and socio-economic circumstances separately but otherwise in order of decreasing power of discrimination. The characteristic of the variables tending to increase the risk is indicated and the ordinal number of the variable in Table 10 is given in brackets.

- Previous low birth weight infants (7)
- Small number of children under 15 years of age (33)
- Advancing age (1)
- Low maternal weight (3)
- Previous abortions (6)
- Small maternal stature (2)
- Low parity (5)
- Long distance to medical officer (47)
- Illegitimacy (9)
- Smoking (26)
- Short distance to centres of population (46)
- Internal migration (42)
- The family has no car (39)
- Mother's occupation belongs to a low social group (10)
- Earlier domicile in remote district (43)

Distributions and mean values of the most important biological variables in the low risk and high risk groups 1—4 are given in Table 21; those of the main socio-economic variables in Table 22. The means were calculated on the cases in which the value of the relevant variable was known; the missing observations were not corrected but these cases were excluded. This provides a descriptive picture of the function of the variables; yet it should be borne in mind that discriminant function analysis is a linear combination of all the variables involved, many variables having a reverse effect on the mean value characteristics of the group. For example, the most potent discriminant in analysis A, previous low birth weight infants, excludes all primiparas. On the other hand, with increasing number of primiparas the mean age of the group is reduced and the influence of advancing age becomes visible after a given parity level. The effect

TABLE 21. Distributions and mean values of biological characteristics among mothers of the low risk and high risk groups formed on the basis of probability classification by discriminant function analysis A of all low birth weight infants

Variables	Low risk groups		High risk groups		Total number of cases
	1	2	3	4	
Percentage with previous low birth weight infants	2.9	5.6	26.3	38.6	8.4
Percentage with previous abortions	14.0	18.6	25.6	25.1	17.0
Primiparae, per cent	24.2	43.9	44.1	32.9	32.7
Mean age of primiparae, years	22.2	22.9	24.1	23.1	22.8
Mean number of children under 15 of para II	0.96	0.94	0.94	0.78	0.95
Mean number of children under 15 of para IV	2.76	2.47	2.51	1.69	2.64
Mothers' mean weight, kg	61.9	56.7	55.2	55.5	59.3
Mothers' mean height, cm	161.2	159.4	157.5	157.4	160.3

TABLE 22. Distributions and mean values of socio-economic circumstances of mothers of the low risk and high risk groups formed on the basis of probability classification by discriminant function analysis A of all low birth weight infants

Variables	Low risk groups		High risk groups		Total number of cases
	1	2	3	4	
Illegitimate, per cent	0.2	3.7	13.2	40.7	5.0
Smokers, per cent	10.2	32.4	40.0	48.0	21.5
Social group I according to the mother's own occupation, per cent	4.2	2.3	1.8	0.7	3.3
Social group IV according to the mother's own occupation, per cent	4.7	6.1	12.1	27.2	6.6
Car owners, per cent	50.1	27.8	21.9	23.1	39.4
Moved to another place of residence, per cent	65.9	67.8	68.4	68.8	66.9
Moved from urban place of residence, per cent of all migrants	9.3	7.5	6.3	11.2	8.5
Moved from remote village, per cent of all migrants	53.9	61.1	73.5	54.2	58.2
Distance to medical officer mean, also, km	15.7	15.8	22.8	23.3	16.7

of a variable may sometimes be seen only if certain other variables remain constant.

A variable of high weighting and consequently high discriminant function, here included in the biological variables, is the number of children under 15 years of age. In the original questionnaire this variable was in-

cluded among the questions measuring the amount of work the mother does. It is, however obvious that the function of this variable is not concerned with working capacity but is a biological characteristic. It contains combined information on parity interval between pregnancies, and deaths of previous

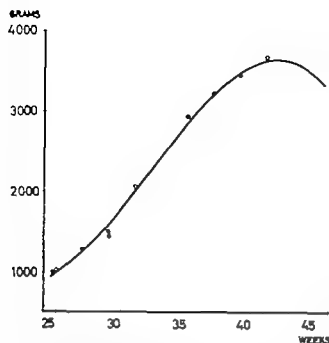


Fig 9 The 50th percentile intrauterine growth curve of the total number of cases and the mean birth weights by week of gestation in the groups obtained from probability classification by discriminant function analysis A which concerned all low birth weight infants.

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The greater the weighting of a variable on the eigenvector, the greater part that variable plays in the discriminant function. There is, however, no specific test to indicate the significance of the weighting.

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- Mother's occupation belongs to a low social group (10)
- Earlier domicile in remote district (43)

Distributions and mean values of the most important biological variables in the low risk and high risk groups 1—4 are given in Table 21, those of the main socio-economic variables in Table 22. The means were calculated on the cases in which the value of the relevant variable was known; the missing observations were not corrected but these cases were excluded. This provides a descriptive picture of the function of the variables, yet it should be borne in mind that discriminant function analysis is a linear combination of all the variables involved, many variables having a reverse effect on the mean value characteristics of the group. For example, the most potent discriminant in analysis A, previous low birth weight infants, excludes all primiparas. On the other hand, with increasing number of primiparas the mean age of the group is reduced and the influence of advancing age becomes visible after a given parity level. The effect

lysis C, the 15 variables with the highest weightings, divided into biological characteristics and socio-economic circumstances but otherwise in descending order of discriminant power are as follows

- Advancing age (1)
- Small maternal stature (2)
- Low parity (5)
- Small number of members in the household (32)
- Low degree of industrialization of the place of residence (40)
- Short distance to centres of population (46)
- Small number of mother's siblings (19)
- No car in the family (39)
- Low level of school attendance (21)
- Sitting work posture of the mother (79)
- Many of the mother's siblings have died (20)
- Mother is employed in service industry (13)
- Long distance to medical officer (47)
- No internal migration (42)
- Non-smoker (26)

The variables essential for the discriminant function of analysis C but absent among the important variables of analyses A and B are small number of mother's siblings, large number of dead siblings, small size of household, low level of school attendance, sedentary work, and employment in a service industry.

Table 23 presents some mean values and

distributions of variables typical of the risk groups of analysis C. Not all cases were classified by analysis C, and for this reason the risk group is represented by only 50 mothers who had given birth to a child with a birth weight of 2500 g or more which had died in the perinatal period, and to whom the analysis had accorded a probability of over 60 per cent of risk group membership. Had the chosen probability level been 50 per cent, 30 per cent of the control cases would have belonged to the risk group for which reason the over-60 per cent probability level was adopted, with which only 16.4 per cent of the controls entered the risk group. The control group in Table 23 consisted of the distribution of variables equalling that in the total number of cases.

If on the basis of the above the important variables of analysis C are reviewed against those of analyses A and B, analysis C is seen to be no more similar to A than B. This conclusion was re-examined by classifying the 119 cases of perinatal deaths with birth weights of 2500 g or more, which made up the risk group of analysis C, using the probability classification of both A and B analyses. With a probability level of 50 per cent or over on analysis A, 22 were placed in the risk group and on analysis B, 21 were placed in the risk group. Hence these two analyses may be considered to place equal numbers from the risk group of analysis C into their respective risk groups. Comparing the effect of analyses A and B on the low birth weight perinatal

TABLE 23 Discriminant function analysis C of perinatal deaths of infants with birth weights of 2500 g or more. Distributions and mean values of characteristics of 50 mothers with 60—100 probability of risk group membership. The corresponding values for all the cases are given

Variables	Included in risk group with 60—100 per cent probability	Total number of cases
Mother's siblings, mean number		
Mother's siblings, mean number of deaths	4.9	5.4
School attendance beyond primary school, per cent of mothers	1.14	0.83
Work mainly sedentary, per cent of mothers	8.1	18.4
Mean development scores of the place of residence	46.1	12.4
	3.7	5.2

children. The question concerned the number of children in a particular mother's household and the reply for mothers living in extended family households also contains information about children other than those of the particular mother herself. In the present study more than 10 per cent of primiparas, who cannot have had children of their own lived in households with children under 15 years of age. In the combined high risk group the percentage was 12 and combined low risk group 15 per cent of primiparas, whereas in the higher parity classes the figure apparently is much lower. Since Table 21 for the mean number of children under 15 in the households of parity 2 and 4 mothers, makes an effort to include the mothers own children only the means have been calculated excluding for parity 2 all figures in excess of one and for parity 4 all figures in excess of 3. This method, naturally has also excluded the mothers with earlier multiple births, but this is of no importance in comparing the means of the different groups.

In discriminant function *analysis B* that is to say the one concerned with the dead low birth weight infants, the following 15 variables had the highest weighting. The variables are again divided into biological characteristics and socio-economic circumstances but other wise they are in the order of importance.

- Small number of children under 15 years of age (33)
- Previous low birth weight infants (7)
- Previous abortions (6)
- Advancing age (1)
- High parity (5)
- Short distance to centre of population (46)
- Long distance to medical officer (47)
- No change of residence (42)
- Illegitimacy (9)
- Place of work as much indoors as outdoors (30)
- Earlier place of residence close to population centre (43)
- Child's father is not farmer (12)

- Running water at home (36)
- Low degree of industrialization in place of residence (40)
- Few rooms at home (34)

The importance of the variables of two discriminant function analyses can be compared by studying the weighting the variables acquire on the eigenvector provided the two analyses have the same power of discrimination and all the variables used are the same. This is true of analyses A and B. In analysis A the weighting of the most important variables is higher than that of analysis B the 15th highest weighting in analysis A was 0.108 in analysis B 0.124. On this basis it may be said that in analysis B the sum of squares which is 1 available for the normalization of the weightings, is divided more uniformly on several variables than in analysis A. For this reason the discrimination significance attributable to the best 15 discriminants in analysis A may be considered in analysis B to divide itself between the 15 variables of the highest 15 weightings and the next 5 which were

- Smoking (26)
- Present place of residence in remote district (41)
- Father makes a living in agriculture (14)
- No television in the family (38)
- Social group according to mother's occupation is low (10)

The significant variables of analysis B which were not essential in analysis A may according to their content be grouped as follows: family makes its living in agriculture but father is not a farmer, the family is destitute and lives in underdeveloped district (variables 12, 14, 30, 34, 38, 40 and 41 in Table 10 page 23).

Analysis C the discriminant function analysis concerned with perinatal deaths with birth weight of 2500 g or more, has a poorer discriminant power than analyses A and B and for this reason the weightings of the variables are not directly comparable. In ana

lysis C, the 15 variables with the highest weightings, divided into biological characteristics and socio-economic circumstances but otherwise in descending order of discriminant power are as follows:

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Mean development score of the place of residence	3.7	5.2

deaths 42.1% were referred to the risk group by analysis B (the particular analysis developed for this group) and 38.4 per cent by analysis A.

Parallel analyses A 1 and B 1 were worked out for analyses A and B using the same control and risk groups while the number and content of the variables was different. 23 variables in the parallel analyses were identical, while A 1 and B 1 contained four variables not present in analyses A and B. The biological variables were identical apart from the number of children under 15. Two of four additional variables measured the mother's attitudes, the third how she felt

about strenuousness of her own work and the fourth measured the father's vocational standing. Fig. 10 shows the distribution of the control and risk group cases in analyses I and B 1 by the probability classification of each of the two analyses. The diagrams illustrate the difference which the added number of variables makes in discriminant power. A study of the weighting of eigen vectors in Table 10 (page 23) revealed that a much smaller number of variables suffice to approach the effectiveness of the discriminant function of analysis B. The weighting of the four variables present only in analysis B 1 were low throughout, as were those of

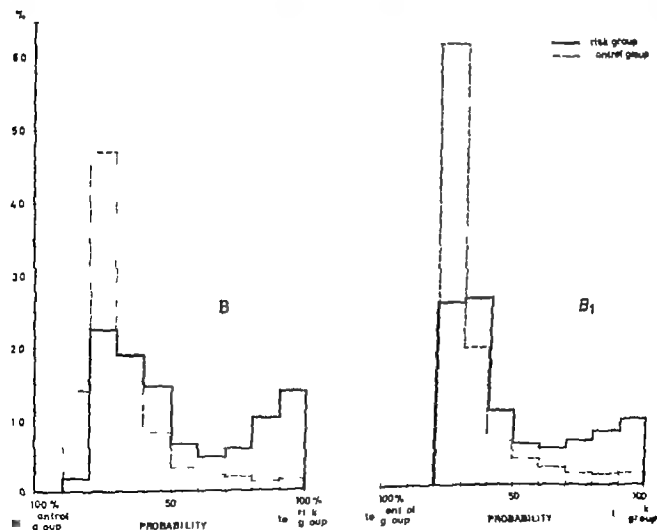


Fig. 10 Percent age distribution of the control and risk group cases on the basis of probability classification by discriminant functions analyses B and B 1.

B is the analysis in which the two groups are controls and low birth weight infants who died (43 variables).

B 1 is the analysis with the same groups but 27 variables.

many variables included in both analyses. On the other hand, analysis B 1 lacked some variables with a relatively high weighting (14, 26, 30, 33, 36, 38, 41 and 47).

In the parallel analyses the order of importance of the variables had undergone little change. Of the 15 variables with the best discriminant power in analyses A and B, 11 were present in analyses A 1 and B 1. In analysis A 1 eight of these were among the 11 with the best discriminant power and in analysis B 1 nine. In analysis A 1 the three variables of minor importance were distance from centres of population, internal migration, and character of the earlier place of residence, which were replaced by intellectual interest, father's occupation and mother's vocational standing. In analysis B 1 the variables distance from centres of population and is father a farmer were replaced by mother's vocational standing and intellectual interest.

The variables are presented in the following classified according to their contents. Some were examined in detail by studying the distributions of the total number of cases. The variables selected for this examination were those whose influence on low birth weight and perinatal mortality had been less studied in earlier literature or for which the earlier results were ambiguous. This method at the same time provides a better picture of the nature of discriminant function analysis.

Biological characteristics Of the eight biological variables (1—8) used in the analysis, six proved essential in analyses of all low birth weight infants and four in those concerned with perinatal deaths of low birth weight infants, whereas in analysis C only age, height and parity were among the variables with the best discriminant power. Age of menarche has but little importance in all the analyses; higher age tends to increase the risk slightly. When all the cases were classified into high risk and low risk groups by analysis A, the mean age of menarche in the high risk group was 14 years 2 months and

in the low risk group 14 years 1 month. Previous perinatal deaths also proved of little importance in these analyses, whereas they had a high correlation to previous low birth weight infants. In analysis A, the high risk group showed perinatal deaths for 12.3 and the low risk group for 3.9 per cent of the mothers.

As mentioned earlier biological characteristics must also include the variables number of children under 15 and perhaps number of members in the household. As a whole, the biological variables played a very important role in the analyses. When the sum of the squares of weightings of variables 1—8 and 33 in each analysis was calculated, the result for analysis A was 0.629, analysis B 0.465 and analysis C 0.433; in other words, the biological variables obtained in analyses A, B and C 62.9, 46.5 and 43.3 per cent, respectively of the total sum of squares of the weightings.

Social standing Of the variables of this group (9—16) the mother's marital status was the most important variable in all analyses concerned with low birth weight infants, while in analysis C it was of no importance. In most analyses, the social classification based on the mother's own occupation proved to possess a slightly better discriminant power than that based on the father's occupation.

Conditions during childhood The four variables describing the mother's childhood background (17—20) held a fairly central position in analysis C, whereas they played a minor role in the analyses concerned with low birth weight infants.

School attendance and intellectual interest This group contained two variables (21—22) of which one, the mother's school attendance, played a part only in analysis C. In the analyses concerned with low birth weight infants, intellectual interest, on average, had a better discriminant power than mother's school attendance.

Attitudes to pregnancy and support by public authorities The three variables of this group (23—25) had very little importance.

deaths 42.1 % were referred to the risk group by analysis B (the particular analysis developed for this group) and 38.4 per cent by analysis A.

Parallel analyses A 1 and B 1 were worked out for analyses A and B using the same control and risk groups while the number and content of the variables was different. 23 variables in the parallel analyses were identical, while A 1 and B 1 contained four variables not present in analyses A and B. The biological variables were identical apart from the number of children under 15. Two of four additional variables measured the mother's attitudes, the third how she felt

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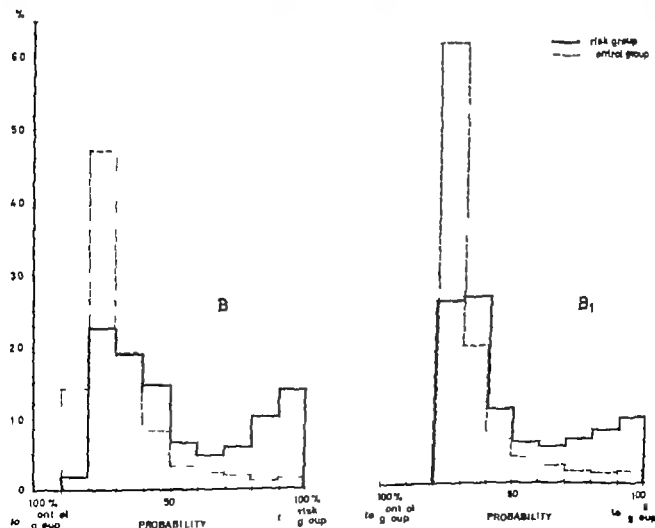


Fig. 10 Percent probability distribution of the control and risk group cases on the basis of probability classification by discriminant function analyses B and B 1

B the analyses in which the two groups are controls and two birth weight variables were used (11 variables)
B 1 is the analysis in which the same groups had 27 variables

birth weight infants they played a less pronounced part. In analyses of perinatal deaths, the absence of internal migration increased the risk. In analyses dealing with all low birth weight infants internal migration was important only in analysis A, whereas in A 1 this variable, though of low weighting, showed a reverse discriminant trend. For this reason, internal migration and present place of residence of all the cases of the series were cross-indexed, with mortality and low birth weight rates calculated on the basis of these variables. The results are presented in Tables 25 and 26. The difference in total mortality rates between those with no change of residence and others who had moved from one place to another was statistically almost significant. Table 25 presents the total mortality rates

vis-à-vis the place of residence, the rate for urban dwellers being the lowest.

The differences in low birth weight rates between those of fixed residence and those who had moved from one place to another were small and of no statistical significance, although the rates of the former were slightly higher (Table 26). The differences according to the type of the current place of residence were also small. In analysis A, that of the low birth weight infants, the nature of the place of residence made no appreciable difference. The fact that internal migration in analysis A emerged as an important variable, increased mobility increasing the risk, was probably due to the variety of groups among the migrating population, the combination of variables selected for the analysis separating

TABLE 25. *Distribution of all cases by internal migration and nature of the current place of residence and the corresponding perinatal mortality rates*

Nature of current place of residence	No internal migration			Migrated			Migration not known			Total		
	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000
Towns	24	993	24.4	49	2,934	16.7	5	97	51.5	78	4,014	19.4
Large village or similar	26	928	28.0	60	2,281	26.3	1	33	30.3	87	3,242	26.8
Remote village	84	1,961	27.3	60	2,599	23.1	2	87	23.0	116	4,647	25.0
Not known	1	1	1000.0	1	3	333.3	0	24	0.0	2	28	71.4
Total	105	3,873	27.1	170	7,817	21.7	8	241	33.2	283	11,931	23.7

TABLE 26. *Distribution of all cases by internal migration and nature of the current place of residence and the corresponding low birth weight rates*

Nature of current place of residence	No internal migration			Migrated			Migration not known			Total		
	Birth weight under 2,500 g. number	Total number of births	Low birth weight rate, per cent	Birth weight under 2,500 g. number	Total number of births	Low birth weight rate, per cent	Birth weight under 2,500 g. number	Total number of births	Low birth weight rate, per cent	Birth weight under 2,500 g. number	Total number of births	Low birth weight rate, per cent
Towns	41	993	4.2	120	2,934	4.1	11	97	11.3	172	4,014	4.3
Large village or similar	37	928	4.0	92	2,281	4.0	3	33	9.0	132	3,242	4.1
Remote village	86	1,961	4.4	105	2,599	4.0	3	87	3.4	194	4,647	4.2
Not known	1	1	100.0	0	3	0.0	0	24	0.0	1	28	3.6
Total	165	3,873	4.3	317	7,817	4.1	17	241	7.1	499	11,931	4.2

Mother's smoking The distribution of all cases by this variable (26) is presented in Table 24 with mortality rates for low birth weight infants and those with birth weights of 2500 g or more of smokers and non smokers. As can be seen from the table, mortality rates were lower in both weight groups if the mother had smoked than if she had not. In the birth weight group of 2500 g or more the difference was statistically significant. The low birth weight rate among smokers was, however, so much higher that the total mortality rates were the same for smokers and non-smokers. In the discriminant function analyses, smoking tended to be associated with the risk group in the two analyses concerned with low birth weight infants, and with control group in analysis C. 21.5 per cent of all the mothers of the series smoked 0.6 per cent smoked pipe, and they were combined with cigarette smokers. Of all mothers of low birth weight babies 32.1 per cent were smokers of the mothers of low birth weight infants whose baby died during the perinatal period 28.4 per cent smoked of all mothers giving birth to infants weighing 2500 g or more, 21.0 per cent were smokers and of the mothers of this birth weight class babies whose baby died during the perinatal period 12.7 per cent smoked.

Work Variables 32 and 33 of this group (27-33) were discussed above among the biological variables. The remaining five were

involved in the various analyses for a total of 16 times and two of the variables were important in two analyses the site of work in analysis B concerning deaths of low birth weight infants, and working posture in analysis C. No variable measuring the amount of work done was significant.

Housing standards These variables (34-37) were of some importance only in analysis I dealing with perinatal deaths of low birth weight infants where the number of rooms and running water were variables with moderate weighting.

Standard of living Of the two variables of this group (38-39) car ownership was an important discriminant factor in analyses A and C, its weighting exceeding that of e.g. mother's or father's occupation. Ownership of a TV set had moderate weighting in analysis B.

Internal migration and characteristics of the present and any possible earlier place of residence The variables of this group (40-47) proved to be important. Of these eight variables, only distance from antenatal clinic and distance from neighbour were unimportant. Distance from medical officer had a high weighting in all analyses which contained this variable, increased distance increasing the risk.

Low degree of industrialization of the place of residence and a remote place of residence increased the risk in analyses of perinatal deaths, while in those concerning all low

TABLE 24 *Distribution of all cases by mother's smoking habits. Perinatal mortality rates for infants of smokers and non smokers separately for low birth weights and birth weights of 2500 g or more*

Mother smoking habits	Birth weight more than 2500 g			Birth weight 2500 g or less			Total number of cases		
	Total number	Number of deaths	Mortality per 1,000	Total number	Number of deaths	Mortality per 1,000	Total number	Number of deaths	Mortality per 1,000
Smokers	2,368	15	6.3	153	44	287.6	2,521	18	23.4
Non smokers	8,898	103	11.6	323	111	343.6	9,221	214	23.2
Not known	166	1	6.0	23	9	391.3	189	10	52.9
Total	11,432	119	10.4	499	164	328.7	11,931	283	23.7

Discussion

1 Material and method

The series of cases was collected from a district where public health facilities lag somewhat behind the general level of the country (162). In 1966 the total perinatal mortality rate in this district was 26.1 per thousand against 22.8 for the whole country (159). Internationally the public health facilities in the district are, however, on a relatively high level. In 1962, for example, the perinatal mortality in England and Wales was 30.8 per thousand (21) and in the United States 27.7 per thousand (156). Although the figures for different countries, owing to the varying definition of the perinatal period, are not fully comparable, the order of magnitude of the rate nevertheless gives an approximate idea (158).

The successful collection of information was essentially the result of the competent antenatal clinic network which has been operating in Finland for more than 20 years, and the small number of home deliveries. Information is lacking on only 4 per cent of the deliveries in the district during the period under review. This percentage may be assumed to represent largely the highest social bracket women who consult private practitioners, and the lowest social bracket women who carry their pregnancies without antenatal care. The results are as complete as such a study can reasonably be expected to attain, and since the sample contained deaths and low birth weight infants in the same proportions as the general population, the deficit does not significantly affect the results.

Of the data concerning the child, the birth weight and survival rate are highly reliable,

whereas the accurate determination of gestational age presents a problem. The normal menstrual cycle varies, and defining the expected date of delivery as 280 days from the first day of the last menstrual period is only an approximation. For women whose menstrual cycle is irregular the exact determination of expected date is difficult. Furthermore, with varying educational level and attendance, recollection of the first day of the last menstrual period is different. Selecting cases on the basis of these criteria would naturally result in a series in which the gestational age would be reliably indicated such a series of cases would, however, be a selected series, both on social and on biological grounds (101-102). Since the present study was one in which biological and social factors were of essential importance, and the purpose was not so much to determine distributions in social and biological optimum material as to analyse a series of mothers in whom these characteristics were the least favourable compared with the total population of a given geographical area, the study tried to reach a compromise between the accuracy of criteria and the number of the cases in which gestational age could be determined. As a result, the number of cases in which the gestational age was unknown, was very small, 3.3 per cent.

The fact that gestational age in a number of cases was determined as being 1-3 days shorter than it really was plays no part in individual cases since the shortening is smaller than the normal biological variation in the duration of gestation. But this deserves to be taken into account when the mean gestational lengths are studied. The effect of this shortening is of an order of 0.76 days (p. 16).

a group for which internal migration did increase the risk.

Distance from centres of population in the 43 variable analyses A B and C had moderate weighting the shorter the distance the greater the risk In analyses A 1 and B 1 this variable had a distinctly lower weighting Since the parallel analyses differed on several points, simple survey did not disclose the definite cause of this type of difference One possible

explanation is, however that analyses A and B contained another variable which measured distance, viz. the distance from medical officer This combination of variables makes possible a more accurate localization of risk groups by distance since, in addition to geographical distance the developmental distance, and any other effect the place of residence may have, can also be measured

Discussion

1 Material and method

The series of cases was collected from a district where public health facilities lag somewhat behind the general level of the country (162). In 1966 the total perinatal mortality rate in this district was 26.1 per thousand against 22.8 for the whole country (159). Internationally the public health facilities in the district are, however on a relatively high level. In 1962, for example, the perinatal mortality in England and Wales was 30.8 per thousand (21) and in the United States 27.7 per thousand (156). Although the figures for different countries, owing to the varying definition of the perinatal period, are not fully comparable, the order of magnitude of the rate nevertheless gives an approximate idea (158).

The successful collection of information was essentially the result of the competent antenatal clinic network which has been operating in Finland for more than 20 years, and the small number of home deliveries. Information is lacking on only 4 per cent of the deliveries in the district during the period under review. This percentage may be assumed to represent largely the highest social bracket women who consult private practitioners, and the lowest social bracket women who carry their pregnancies without antenatal care. The results are as complete as such a study can reasonably be expected to attain, and since the sample contained deaths and low birth weight infants in the same proportions as the general population, the deficit does not significantly affect the results.

Of the data concerning the child, the birth weight and survival rate are highly reliable,

whereas the accurate determination of gestational age presents a problem. The normal menstrual cycle varies, and defining the expected date of delivery as 280 days from the first day of the last menstrual period is only an approximation. For women whose menstrual cycle is irregular the exact determination of expected date is difficult; furthermore, with varying educational level and attendance, recollection of the first day of the last menstrual period is different. Selecting cases on the basis of these criteria would naturally result in a series in which the gestational age would be reliably indicated such a series of cases would, however be a selected series, both on social and on biological grounds (101-102). Since the present study was one in which biological and social factors were of essential importance, and the purpose was not so much to determine distributions in social and biological optimum material as to analyse a series of mothers in whom these characteristics were the least favourable compared with the total population of a given geographical area, the study tried to reach a compromise between the accuracy of criteria and the number of the cases in which gestational age could be determined. As a result, the number of cases in which the gestational age was unknown, was very small, 3.3 per cent.

The fact that gestational age in a number of cases was determined as being 1-3 days shorter than it really was plays no part in individual cases since the shortening is smaller than the normal biological variation in the duration of gestation. But this deserves to be taken into account when the mean gestational lengths are studied: the effect of this shortening is of an order of 0.76 days (p. 16).

The multi variable analysis chosen for the statistical treatment of the data, the discriminant function analysis was more practicable for the study than a factor analysis since it provides a possibility of classification and more practicable than the regression analysis since a probability classification does not require that the characteristic classified be measurable on a continuum

On the basis of the present results it is impossible to say whether better results could have been obtained using a battery of variables, all of which were normally distributed and continuous.

A study of groups with different degrees of risk based on probability classification provides the answers to the questions posed. Abernathy et al used a different modification of discriminant function analysis (the discriminant function was calculated via multiple regression and the groups were given fixed numerical values for the dependent variable) to find the factors discriminating between the survivals and the perinatal deaths (3) The variables included some of those used in the present study but also information on the course of pregnancy (blood pressure haemoglobin etc) and in some analyses the child's birth weight length at birth and gestational age were among the variables. For all these reasons, the results are not comparable The findings reported by Abernathy et al according to which the other variables do not essentially increase the discriminant power obtained from the child's birth weight length at birth and gestational age (3) is not particularly surprising the essential problem in perinatal mortality being low birth weight and low gestational age

The aim of a prospective study was well achieved The fact that the questionnaires concerning perinatal deaths of low birth weight infants were completed before delivery in only 70 per cent of the cases, does not seem to have affected the results.

The method used for supplying the missing data gives an adequate correction as long as

the true values of the missing data have the same distribution as the recorded data. If the assumption holds good that the reply has been omitted most often when it would have been in the negative then the existence of missing data increases classification bias for a few variables The most important individual variable of this type is the existence of previous low birth weight infants in analyses of low birth weight babies. Among the controls, this was the question most frequently left unanswered it was unanswered in 10.7 per cent of the cases Since in the group of control cases, 7.6 per cent of the recorded replies were in the affirmative this percentage of the missing replies is supplied in the affirmative. Should all missing replies in reality have been in the negative the false positive answers among a control population of 10 000 cases would have numbered 81. From the point of view of the total result, not even this possible classification error can be considered vital The discrimination of groups would of course be more complete if the recorded data were more complete

2 Variations in and correlations of birth weight and gestational age

The present results reveal the vast variations in birth weight even at identical gestational ages (Table 27 in Appendix 2) The variation has the relatively widest range in the early weeks of gestation a finding which agrees with that reported by other authors (14 45 62 77 102 141)

Of the 468 low birth weight infants in the present series of known gestational age 67 per cent were pre-term by their gestational age (Tables 2 and 3) The literature reports that 48—66 per cent of the low birth weight infants had a gestational age not exceeding 37 weeks (8 21 141 171) a percentage well in agreement with the present finding Although gestational age cannot be determined as accurately as birth weight, research

workers in this field today agree that even a child born at term may have a birth weight considerably below 2500 g. On the other hand some research workers express their doubts as to whether the relatively widest range of variation in birth weights in the early weeks of gestation is real. Gruenwald and Neligan have devoted particular attention to the problem (62, 102). In his studies of the birth weights of infants born in the 28th to 34th weeks of gestation, Gruenwald found that they showed a bimodal distribution (62) and Neligan in his series of cases arrived at the same result (102). They combined this finding with the clinical observation that many women, in early pregnancy had bleeding which may have been misinterpreted as the last menstrual period before pregnancy. The gestational age of babies born would therefore in reality be higher than the calculated age. On this basis, Gruenwald corrected his intrauterine growth curve by deleting up to the 34th week of gestation the lower peak which represented the higher weight class in bimodal

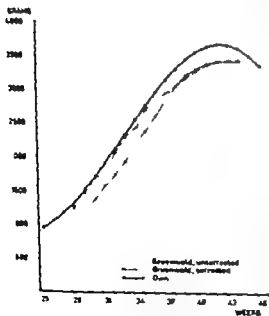


Fig. 11 The 50th percentile intrauterine growth curve of the present series of cases together with Gruenwald's corrected and uncorrected curves.

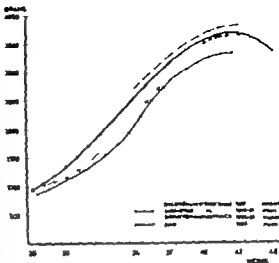


Fig. 12 The 50th percentile intrauterine growth curves based on the present findings, together with curves by a few other authors.

distribution and correcting the 34th to 37th week interval by extrapolation from the values at the beginning and end of the curve. Fig. 11 shows Gruenwald's corrected and uncorrected intrauterine growth curves together with the curve concerning the present series of cases.

The best method of calculating the values of the growth curve is naturally extremely difficult to decide. The intrauterine growth curve based on birth weights of pre-term infants by no means represents a normal foetal population, since prematurity in itself is a nonphysiological condition (47 134 136); this does not, however prevent studies of pathological conditions. But this means that the distribution of the birth weight for pre-term babies may include a larger proportion of extreme values compared with the intrauterine weight of unborn babies. The bimodal distribution of birth weights at the early weeks of gestation found by Gruenwald and Neligan would be replaced by a unimodal distribution if the intrauterine weight of term babies could be measured at that time.

Fig. 12 presents a number of intrauterine growth curves reported by various authors,

together with the curve based on the present series. The curve of Lubchenco et al. (86) is well known it is based on data collected at a Colorado Hospital a place 5 000 feet above sea level. In addition stillbirths and infants with severe deformities had been removed from the series, as had infants considered too large for their gestational age. Most of these factors would tend to flatten the curve. The other two curves on the diagram have been published in national publication series for practical pediatrics but they are of interest here as one is based on Swedish and the other on Finnish data. Engström and Sterky's initial series covers some 85 per cent of all births in Sweden during one year but the criteria laid down for both maternal and foetal illnesses and for calculation of gestational weeks have caused so many deletions that the growth curve is really based on only just over 60 per cent of the initial series (38). Since the growth curve values of Fig. 12 were taken for the present work from a drawing they may not be exact. The curve in the figure is the boys curve the curve for girls had a course very similar to that based on the present series. In addition to that of Engström and Sterky there is just another Swedish intrauterine growth curve which after the 38th week runs a higher course than the present curve (83). Prior to the 36th week of gestation birth weights reported by Karn and Penrose (77) Taback (141) Fraccaro (45) and Neligan (102) exceeded those based on the present series.

The differences between the intrauterine growth curve by Bäckström and Kauppinen (24) and the present curve are interesting, since the former is based on Helsinki mothers — all urban dwellers — while only one-third of the present series lived in towns. Term births in the series by Bäckström and Kauppinen had somewhat lower birth weights but since the parity distribution of the mothers was very probably different, it seems that had parity been fixed the birth weights of Helsinki babies would be equal to or slightly

higher than those of the present series. The differences, however, were considerably more pronounced from the 28th to the 37th week of gestation. This may of course be partly due to the different mathematical treatment of data, but there is no proof that the etiology of pre-term births might not show geographical differences affecting intrauterine growth rates.

The higher mean birth weight of boys is well known and visible in all series. In the present data the mean birth weight of boys exceeded that of girls by 118 grams. The shorter duration of boy pregnancies is apparent in many reports (45, 77, 148) in the present series it was, on average, 11 days shorter than that of girl pregnancies (page 16).

The boy/girl ratio of the total number of cases is unusually high 1086/1000. In an international survey covering seven countries and all births over 15 years, the highest ratio 1079 applied to Sweden in 1956 (158). According to the paper in countries with a high boy/girl ratio such as Sweden and the Netherlands, perinatal mortality rate is low. Some authors have associated the high boy/girl ratio with a cold climate, claiming that more boys were conceived in the cold season (111). Timonen, in his studies covering the years 1957–58 found that the boy/girl ratio in North Finland was statistically significantly higher than in South Finland (149). The boy/girl ratio 1150 from Korea reported by Kang and Cho ranks among the highest in the literature (76). The higher proportion of boys among the cases is, from the overall point of view sufficiently negligible not to affect the mean birth weight or gestational age.

3 Perinatal mortality rate correlated with birth weight and gestational age

The correlation between the perinatal mortality rate and birth weight (Table 28 in

Appendix 3 Fig. 5) is parallel to that reported in earlier population studies (14-39): the mortality rate falls steeply from the lowest towards the higher weight groups but increases again slightly in the highest weight groups. Studied by 200 gram weight groups, the mortality rate was lowest between 3500-3699 grams by the customary 500 gram weight groups it was lowest between 3500-3999 grams (4.9 per thousand). The weight group with the lowest mortality therefore, is only slightly above the mean birth weight of all the cases, 3440 grams, and coincides with the most frequent weight groups. In these weight groups, the mortality rate is thus only about one-fifth to one-seventh of that of all the cases. If gestational age is simultaneously taken into account, the mortality rate of the most favourable group is only about one-tenth of that of all the cases, although such a group covers a good 40 per cent of the cases (115). In studies of neonatal mortality the weight group representing the lowest mortality rate has usually been well above the mean birth weight level (45-77-131), but as a rule the most favourable weight group has been the same as in the present study and the difference is due to the lower mean birth weight of the other reports.

The correlation of perinatal mortality with gestational age also corresponds to the earlier population studies (14-39). In the present study the mortality rate was lowest in the 40th week of gestation, which is compatible with other authors' results.

When the risk of perinatal death is reviewed two-dimensionally in relation both to birth weight and gestational age (Table 7), there are certain differences from a similar study by Butler (22). He studied only cases from 36 (full) weeks of gestation onwards, using standard deviations instead of percentiles. The results are parallel in that the mortality rate is lowest above the curve representing the mean birth weight, in the present study

between 50-90 percentiles and in Butler's study between standard deviations of 0-+2, rising steeply below this range. Butler also reports, however a definite rise in mortality roughly double, when +2 SD is surpassed, while in the present survey mortality in the over 90 percentile range rose only in the pre-term group. This difference may be explainable because +2 SD weighs more heavily against extreme cases than the 90th percentile, and corresponds to about the 98th percentile. In that case the difference, however might also be expected to be larger among infants below -2 SD but Butler's mortality rate 68.5 per thousand under -2 SD is very close to the combined mortality rate for term and post-term babies of the present series, which was 61.7 per thousand. The finding can be explained from the different overall mortality rates of the two series for the British series, collected 8 years earlier it was 33.6 per thousand against 23.7 per thousand for the present survey. Other authors have found that a fall in perinatal mortality rates in recent years was concerned mainly with infants of birth weights exceeding 2500 grams (13-29). This finding, when applied to the problem under discussion, suggests that the mortality of babies below the standard deviation range has not changed, while that above this range shows differences which depend on when the cases were collected. In the range of 50-90 percentiles the mortality of term and post-term babies in the present study was 5.6 per thousand, while in the British study within the range 0-+1 SD it was 7.3 and within the range +1-+2 SD it was 8.6 per thousand, that is to say about 40 per cent higher within the range 0-+1 SD in the present study. But the mortality rate for births below the standard deviation was only 11 per cent higher in the British study which suggests that the mortality is more small for these periods up to the present roughly comparable with that in the present series as reported.

The present study is a survey of the

intrauterine growth curves cannot, however be disregarded. Butler was unable to determine the gestational length in 13 per cent of his cases while the birth weight was unknown in 5 per cent. In the present study the 3 per cent whose gestational length was unknown had both a mortality rate and low birth weight rate twice that of the total number of cases, and on this basis some group might be assumed to be over represented among the cases falling outside the investigation. A more important difference however is that Butler excluded all macerated stillbirths and major congenital anomalies which clearly influenced weight for given gestation. In Butler's series macerated stillbirths accounted for some 30 per cent of all deaths and some 50 per cent of all stillbirths (21). Exclusion of these cases was naturally due to the fact that autolysis is associated with weight loss in the course of time and when efforts were made to obtain the most accurate results possible such cases were excluded. For the relative distribution of perinatal mortality over the intrauterine growth curve this naturally makes no difference unless stillbirths are associated with biological factors producing intrauterine weight increase different from that of later deaths. There is reason to assume, however that placental insufficiency is more frequent among the stillbirths than the others (58-60) and on this basis the birth weights of this group would differ from those of the others. Hence Butler's series would exclude a relatively higher proportion of perinatal deaths located below the mean intrauterine growth curve.

In the present study the interest is focused on intrauterine growth which falls below the normal level and the accompanying increased perinatal mortality. For this reason a large number of the stillbirths could not be excluded from the analysis. The weight loss during autolysis is probably restricted to a few hundreds of grams whenever the rule of obstetric treatment in cases of foetal death is to induce labour as soon as possible, whereas

the total distribution in birth weights in most groups of gestational length is several thousands of grams.

Table 9 reviews the mean birth weights of infants who died in different phases of the perinatal period with especial regard to the weight loss during autolysis of stillbirths. Deaths during delivery were combined with neonatal deaths, since hardly any measurable weight loss has time to occur. The study of British Perinatal Mortality recorded maceration in 13 per cent of the deaths during delivery but maceration alone does not imply weight loss. It is impossible to say to what extent the lower mean weight of babies who died before the start of delivery compared with those who died later was a result of weight loss during autolysis and to what extent it was due to other causes of death apparently there was a combination of both groups of causes. Table 9 reveals, however that all perinatal deaths were markedly smaller for their gestational age than the survivals. As can be seen from Fig. 7 the inclusion of foetal deaths did not appreciably affect the values of the 50th percentile of the intrauterine growth curve, but it is probable that exclusion of these cases would imply a changed distribution of perinatal mortality over the different areas of the intrauterine growth curve.

The higher perinatal mortality of pre-term high birth weight infants has been reported earlier (14-16). As already mentioned, the true gestational age of these babies was discussed by Gruenwald and Neligan. Increased mortality may naturally be taken to indicate that these infants really were pre-term births and that the increased mortality was due to prematurity. Another explanation as advanced by Battaglia is that the gestational length in these cases may have been incorrectly estimated owing to a bleeding during pregnancy and that this bleeding would at the same time have injured the foetus, causing increased perinatal mortality (14).

4 Perinatal mortality and birth weight correlated to maternal biological characteristics and socio-economic circumstances and prediction of the former from the latter

a. The child's characteristics in identified risk groups

The mean values of the birth weights and lengths at birth of low risk and high risk groups formed on the basis of the probability classification of analysis A, which dealt with all low birth weight infants, can be compared with the corresponding mean values of the total or partial populations of different countries. The birth weight 2970 g and length 48.1 cm of the highest risk group 4 (Table 16) agree with those reported by Ghosh from India in 1959—61: 2720 g and 48.3 cm, respectively (51). Ghosh's series did not contain stillbirths, but its neonatal mortality was 35 per thousand. Since stillbirths usually equal about half the perinatal mortality (Table 1), the perinatal mortality rate of 72.4 per thousand of the risk group (Table 15) also agrees with the Indian series. The low birth weight rate in the present risk group was 22.0 per cent and in the Indian series 24.2 per cent (52).

In the next highest risk group 3 the mean birth weight was 3180 g and perinatal mortality 44.1 per thousand. In 1962 the mean birth weight of U.S. Negro children was 3140 g (155) and perinatal mortality 56.2 per thousand (156). The low birth weight rate in risk group 3 was 9.2 per cent and among U.S. Negroes 13.1 per cent (155).

The low risk group 2 agrees best with the mean values of the present series. The low risk group 1 with a mean birth weight of 3544 g and length at birth of 50.6 cm, corresponds to the Swedish series of 1956—57 published by Engström and Sterky with a

mean birth weight of 3500 g and length at birth of 50.9 cm (38). The perinatal mortality rate in Sweden in 1965 was 19.6 per thousand (113), and that of group 1 16.2 per thousand. The low birth weight rate in Sweden is, however, around 5 per cent (158), whereas in the present group 1 it was 1.9 per cent. No geographical population corresponding to the mean birth weight — 3770 grams — of the minimum risk subgroup separated within the low risk group 1 has been reported anywhere.

Although the battery of variables used in the discriminant function analysis assembled in the high risk groups a few characteristics, e.g. the low parity not typical of the Indian or the U.S. Negro parturient populations serving for comparison, the high risk groups of the present series differed on many of the variables used from the total series in the same direction as the control populations e.g. from the Swedish series.

It is interesting that the birth weights and lengths at birth, and perinatal mortality rates, in the compared studies agreed relatively well, but in a natural population the low birth weight rate does not fall as low as in the lowest risk group.

The literature reports several studies on the differences in mean birth weights and low birth weight rates between the children of populations of two or more races living in the same geographical area (15, 31, 39, 53, 71, 126, 127, 174). A general finding is that the races in which children's mean birth weights are lower live in poorer socio-economic circumstances.

The part played by genetics in determining birth weight and length at birth has been examined by twin studies, studies of consanguineous parents, and comparisons of sister-sister and brother-brother pairs (47, 50, 97, 98). Even though the foetal genotype does affect the size of the infants born, it seems that only a minor proportion of the total variance of birth weights is determined genetically while a considerably higher propor-

tion is governed by the parents socio-economic circumstances and actual biological status

When the differences in mean birth weights between the high risk and low risk groups in different gestational weeks are compared in Table 20 and Fig. 9 with the corresponding differences between girls and boys in Table 6 the differences between risk groups are found to exceed those between girls and boys. The difference in mean birth weights between risk groups is 366 g, while that between girls and boys is 118 g. The birth weights of the low risk group are higher from the 29th—30th gestational weeks whereas the birth weight of boys exceeds that of girls regularly only from the 33rd—34th gestational week onwards.

The difference in intrauterine growth rate between high risk and low risk groups was thus demonstrable from the 29th—30th gestational week onwards. This finding differs from Gruenwald's assumption according to which differences in birth weights due to various causative factors — chronic foetal distress, maternal diabetes, twin pregnancy or racial (probably economic and nutritional) factors — do not emerge with statistical significance before the 34th gestational week (61).

When the theory suggesting that the duration of gestation of high birth weight — low gestational age infants might have been mis-calculated is reviewed in this connection it seems hardly probable that the mothers of the low risk group who on average have a better social standing would report the date of their last menstrual period less accurately. On this basis it may be assumed that the intrauterine growth curves of different parturient populations in the early gestational weeks really are different. Were the cases more numerous and had the multi variable analysis been designed to discriminate the growth retarded infants, the differences might perhaps be visible even earlier. In the present study the high risk group was not composed exclusively of infants small for their calculated term, as

can be seen from Table 19. Ounsted studied the characteristics of mothers of growth retarded infants and came to the conclusion that low birth weight infants born after short gestation with average birth weights in view of their gestational age constitute an entirely different biological group from those low birth weight infants whose intrauterine growth was retarded (104). The mothers of the latter group according to Ounsted, were likely to give birth again to a similar infant, whereas the low birth weight representing the average intrauterine growth phase lacked this likelihood of recurrence.

When the intrauterine growth rates of Helsinki and North Finnish infants are re-examined against the above background (Fig. 12), one may speculate whether or not the low birth weight infants of the Helsinki population of mothers contained relatively more with retarded growth than those of North Finland. In a population of mothers with a high mean parity in which family planning has not yet been generally accepted, pathologic groups representing high birth weights, such as maternal diabetes and Rhesus incompatibility may assume a dominant position compared with the relative number of low birth weight infants.

The high risk group contained statistically significantly fewer boys than the initial series: the boy/girl ratio for the former was 910 and for the latter 1086 per thousand. All series of low birth weight infants with the group limit set at a given birth weight unfailingly contain more girls since the mean birth weight of girls is lower. The variables used to classify a number of the present cases into risk group had nothing to do with the child's birth weight but concerned maternal characteristics, for which reason the explanation must be sought elsewhere. Ounsted when examining infants of retarded intrauterine growth looked into whether their mothers were disposed to bearing a higher proportion of girls than the normal distribution presupposed (104). She also examined infants of

above-average intrauterine growth and tried to discover whether their disposition to have more boys than girls differed from the normal distribution (105). She was unable to prove such a disposition in either case. The present finding that high risk groups contained fewer boys may of course have its explanation in that, for some reason or other, abortions are more frequent in boy than girl pregnancies.

b Importance of maternal characteristics in different risk groups

The mother's parity is known to be positively correlated with the birth weight of the expected child (45 72, 77 127 148 149 157) whereas correlation between gestational length and parity is low (45 82, 148, 149). Karn and Penrose found that gestational length was slightly less in the higher parity groups (77). In the present study low parity also tended to increase the risk in analyses in which the discriminated group was composed of all low birth weight infants.

If the risk of perinatal mortality is shown on a curve against parity the curve will be U-shaped. The risk is highest for primiparas and increases again from parity 4 upwards (21 34 40, 64 72, 93). In analyses with perinatal mortality cases functioning as the groups to be separated, parity has a moderate weighting, low parity tending to increase the risk. In analysis II however high parity increased the risk. The variable number of children under 15 which also partly covers the concept of parity in this analysis increased the risk when the number of children under 15 was low.

The positive correlation between maternal age and perinatal mortality is also a known fact (21 34 40 64 72, 93). Mortality has been found to increase with age especially after the age of 35 (21 34). Feldstein, with a binary variable multiple regression analysis, studied the effect of maternal age on perinatal mortality (41). He found that the perinatal mortality rate for mothers aged under 20 was 6.7

per cent higher than that for the whole series, but after the effect of parity and socio-economic circumstances was eliminated the mortality was 11.8 per cent below the mean value. The risk of perinatal mortality was smallest if the mother was 20-24 years old, after the elimination of the effect of parity and social group. With mothers aged 25-29 years, favourable parity and social group usually reduced the risk, but after these factors were eliminated the risk was higher than among those under 20 years of age. For mothers aged 40 years or more the elimination of other factors had little effect on the risk of perinatal mortality and the risk was twice that of the middle of the series. With primiparas, favourable age could usually be taken to reduce the risk resulting from their parity rating.

In the present study advancing age, in all analyses, both those concerned with birth weight and with perinatal mortality tended to increase the risk. This variable was relatively of the greatest importance in the analysis concerning perinatal deaths with birth weights of 2500 g or more.

The correlation of maternal height with the infant's birth weight has been studied by many authors, and the correlation has been positive (10 17 25 75 84 92, 143 144 146). In the present study a mother's shorter stature increased the risk of low birth weight infants and of perinatal mortality. Earlier authors also found that infants of short mothers had a higher perinatal mortality rate (21 75 146). Adult height is considered to be the combined result of the individual's genotype and socio-economic environment during childhood, in that genes determine the potential height while actual height depends largely on nutrition, health, etc. during the period of growth besides genes (21 23 70, 79 142).

The mother's weight is not a constant like height, but reflects her size, structure and her nutritional condition, and in extreme cases disease. In the present study the mother's weight was more important in analyses A

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a higher weighting than body weight. Love and Kinch found in their study that mother's weight before pregnancy was better correlated with the child's birth weight than maternal height (84). Many authors have found that mothers of lighter weight had children of lower birth weights (9 146 149 150). On the other hand obesity has been found to increase the low birth weight rate (42).

The correlation of maternal weight with perinatal mortality is less obvious. In the discriminant function analysis reported by Abernathy et al. increasing weight suggested increased perinatal mortality rate (3) while Kaltreider failed to trace any correlation between perinatal mortality and maternal weight (75). Sauramo studied abnormally high and low weights among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128). Fusher and Frey by contrast noted no increase in the foetal mortality rate among overweight mothers (43).

Menarche age is correlated to the socio-economic environment in that the age of menarche is better socio-economic circumstances is lower (135). On the other hand age of menarche has been found to have correlations, interpreted as genetic, in mother-daughter and sister-sister pairs (50). In the present study the age of menarche did not discriminate between the controls and the groups to be separated.

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated. The result was parallel to those of earlier studies (20 21 49 138).

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants, whereas in that of perinatal deaths with birth weights of 2500

g or more this variable had no appreciable importance. Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20 21 49 11, 104 167). In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth weight was the result of intra uterine nutrition but not when it was due to premature delivery (104).

Previous perinatal mortality did not indicate increased risk in any of the present analyses. Since previous perinatal mortality is markedly correlated with previous low birth weight infants, the distribution of this variable, too, was different in the high risk and low risk groups of analysis A. In the British perinatal mortality study the correlation of previous perinatal mortality with the present mortality was more pronounced than that of previous low birth weight infants and previous abortions (21).

The number of children under 15 is a variable which covers both parity interval between pregnancies and number of children who had died before the age of 15. As pointed out before the question is phrased so that it includes, wherever mothers live in extended-family households, children other than the mother's own. Component factors are known to exert a parallel effect: the expected child's prognosis is made worse by low parity as shown above (p 47), long intervals between pregnancies (163) and deaths of earlier children. It is also possible that the sphere of life associated with extended family households tends to reduce the risk. Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154 158). It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used compared with the variable subsuming the whole childhood mortality rate, can be explained against this background.

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

along with perinatal deaths with birth weight of 2500 g or more. The finding was contrary to that reported from Great Britain where the perinatal mortality rate of illegitimate children was clearly higher for even this low birth weight group (21). In the same study the low birth weight rate among illegitimate children was also higher. In many other countries illegitimacy has been found to increase perinatal mortality for example in Denmark (158) and in Finland too similar results have previously been reported (7, 109). Society in general has become more tolerant towards illegitimacy and it is possible that the widely differing percentages of unmarried mothers in different countries reflect different attitudes to the issue. In Sweden the percentage of unmarried mothers, 13 per cent in 1964 is considerably higher than in many countries (158), and it is interesting to see how changed attitudes will be reflected in the prognosis of children born out of wedlock. Parmelee found from his studies that unmarried mothers, whose antenatal care was well organized, had the same low birth weight rates as the total population (107).

In the present study social and economic standing was analysed by means of a large number of variables (Table 10). Variables classified to indicate social status, housing level and standard of living are here discussed together since on the basis of the present results they cannot be considered to possess any importance as groups. The second best discriminant factor after marital status is ownership of car. According to West, in Finnish rural communes automobile density is growing faster than the economical variables upon which it depends (164). According to the present study too, car ownership appears to be a more dynamic variable than e.g. the mother's or father's social class.

With the combination of variables used in the present study social classification based on the mother's occupation seemed to possess, on average, a slightly better discriminant

power than that based on the father's occupation.

Irrespective of how the socio-economic level was measured, its low level tends to increase the risk of both low birth weight and perinatal mortality. Authors in different parts of the world have arrived at parallel results on this point (10-12, 15, 18, 21, 35, 54, 71, 72, 110, 117, 119, 126, 132, 133, 145, 147, 163, 165, 166). In the present study economic factors increased the risk of perinatal deaths of low birth weight infants. This finding was contradictory to that reported by Ahvenainen and Kunnas in their study of hospital cases the neonatal mortality of low birth weight infants was slightly higher for the higher social class infants (7). When these studies are compared it should be borne in mind that the present series also included prenatal deaths, and that there may be differences between the social classes as regards readiness to seek medical advice for children.

Variables illustrating the circumstances during childhood were more important in the analysis concerned with perinatal deaths of infants with birth weights of 2500 g or more than in the other analyses. The most prominent discriminant factor increasing the risk was small number of mother's siblings: a finding contradictory to that of the British study according to which perinatal mortality rate increased in direct proportion to the number of mother's siblings and was visible in all social classes (79). Within the framework of the present study it cannot be said whether size of family as a risk increasing factor should be associated with the relatively high degree of segregation of the population living in the region studied, with the consequence that there might be an increased incidence of conditions due to the meeting up of harmful recessive genes, but this possibility does exist.

Social classification based on the occupation of the child's parents was more important in the present study than that based on the occupation of the child's maternal grandfather. The finding is contradictory to that reported

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a higher weighting than body weight. Love and Kinch found in their study that mother's weight before pregnancy was better correlated with the child's birth weight than maternal height (84). Many authors have found that mothers of lighter weight had children of lower birth weights (9, 146, 149, 150). On the other hand obesity has been found to increase the low birth weight rate (42).

The correlation of maternal weight with perinatal mortality is less obvious. In the discriminant function analysis reported by Abernathy et al., increasing weight suggested increased perinatal mortality rate (3) while Kaltreider failed to trace any correlation between perinatal mortality and maternal weight (75). Sauramo studied abnormally high and low weights among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128). Fisher and Frey, by contrast, noted no increase in the foetal mortality rate among overweight mothers (43).

Menarche age is correlated to the socio-economic environment in that the age of menarche in better socio-economic circumstances is lower (135). On the other hand, age of menarche has been found to have correlations, interpreted as genetic, in mother-daughter and sister-sister pairs (50). In the present study the age of menarche did not discriminate between the controls and the groups to be separated.

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated. The result was parallel to those of earlier studies (20, 21, 49, 138).

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants whereas in that of perinatal deaths with birth weights of 2500

g or more this variable had no appreciable importance. Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20, 21, 49, 104, 167). In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth weight was the result of intra-uterine nutrition but not when it was due to premature delivery (104).

Previous perinatal mortality did not indicate increased risk in any of the present analyses. Since previous perinatal mortality is markedly correlated with previous low birth weight infants, the distribution of this variable, too, was different in the high risk and low risk groups of analysis A. In the British perinatal mortality study the correlation of previous perinatal mortality with the present mortality was more pronounced than that of previous low birth weight infants and previous abortions (21).

The number of children under 15 is a variable which covers both parity interval between pregnancies, and number of children who had died before the age of 15. As pointed out before the question is phrased so that it includes, wherever mothers live in extended family households, children other than the mother's own. Component factors are known to exert a parallel effect: the expected child's prognosis is made worse by low parity as shown above (p. 47), long intervals between pregnancies (163), and deaths of earlier children. It is also possible that the sphere of life associated with extended family households tends to reduce the risk. Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154, 158). It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used, compared with the variable subsuming the whole childhood mortality rate, can be explained against this background.

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

dealing with perinatal deaths with birth weight of 2500 g or more. The finding was contrary to that reported from Great Britain where the perinatal mortality rate of illegitimate children was clearly higher for even this birth weight group (21). In the same study the low birth weight rate among illegitimate children was also higher. In many other countries illegitimacy has been found to increase perinatal mortality for example in Denmark (158), and in Finland too similar results have previously been reported (7, 109). Society in general, has become more tolerant towards illegitimacy and it is possible that the widely differing percentages of unmarried mothers in different countries reflect different attitudes to the issue. In Sweden the percentage of unmarried mothers, 13 per cent in 1964 is considerably higher than in many countries (158), and it is interesting to see how changed attitudes will be reflected in the prognosis of children born out of wedlock. Parmelee found from his studies that unmarried mothers, whose antenatal care was well organized, had the same low birth weight rates as the total population (107).

In the present study social and economic standing was analysed by means of a large number of variables (Table 10). Variables classified to indicate social status, housing level and standard of living are here discussed together since on the basis of the present results they cannot be considered to possess any importance as groups. The second best discriminant factor after marital status is ownership of car. According to West, in Finnish rural communities automobile density is growing faster than the economical variables upon which it depends (164). According to the present study too, car ownership appears to be a more dynamic variable than e.g. the mother's or father's social class.

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ment outside the home on either low birth weight rate or perinatal mortality (37 48, 69).

In the analysis of perinatal deaths of small birth weight infants, the mother's site of work was of some importance, and it is possible that this is associated with the strenuousness of the work. Ahvenainen and Kunas came to the conclusion that in birth weight group 1500-2000 grams strenuous work seemed to increase neonatal mortality (7).

In the analysis concerning perinatal deaths of infants with birth weights of 2500 g or more the mother's posture at work played some part in that sedentary work tended to increase the risk. This finding, perhaps, may be connected with placental circulation (78, 125).

The level of industrialization in the community was of the greatest importance only in the analyses of perinatal deaths. The regional developmental level in Finland is associated with the degree of industrialization, the less developed regions being predominantly agricultural no industrial firms exist in Finland. The indicators used to measure the degree of industrialization were the income level (taxable income of private persons per capita) the degree of industrialization (the ratio (%) of those engaged in industry to total economically active population) the degree of industrialization (number of wage earners and salaried employees engaged in industry per 1,000 inhabitants) the ratio (%) of those engaged in agriculture and forestry to the total population the financial position of the commune the density of population (resident population per sq. km of land area) the degree of electrification (the ratio (%) of dwellings equipped with electricity to total dwellings) cars per 1,000 inhabitants the ratio (%) of those born in the commune to the total corresponding age groups the ratio (%) of those with a middle-school background to the corresponding age groups the ratio (%) of those engaged in the service industries (in addition to services proper commerce, storage, transport, and communications) to total econo-

mically active population the ratio (%) of those living in non-administrative urban settlements to the total population the ratio (%) of the dwellings equipped with water pipes to total dwellings the length of public highways relative to the land area the mean cultivated area of farms with at least 2 hectares of arable land migration (balance of migration per 1,000 of mean population) home lending by public libraries (books per capita) infant mortality (infant deaths per 1,000 live births) (106).

The nature of the community urban/rural also has a high discriminant power in analyses of perinatal deaths. Regional fluctuations in mortality are well known, and comparisons have been made between countries (140, 154 158), between different regions (21 162) and between sectors of one region having different degrees of development (35 166) In the less developed regions mortality rates are usually higher. In international comparisons, however infant mortality and perinatal mortality are no longer directly correlated with the national income level. This is particularly noticeable in the United States where infant and perinatal mortality rates today are definitely higher than in many countries of Western Europe (140, 158). The causes of this difference are far from obvious, since mortality rates lower than those of the United States are now recorded even in many countries where the rates in the early decades of the 20th century were considerably higher than in the United States. Research into the differences in perinatal and infant mortality between countries has been able to suggest only two explanations for the lag of the United States, viz. the different distribution of birth weights, the low birth weight rate being higher in the United States, and the contrast in the financing and administration of medical care (158).

The variable internal migration separates the groups of perinatal deaths from the control group distinctly nonmigration being characteristic for the risk group, whereas

by Drillen in whose study the occupation of the mother's father was better correlated with low birth weight rate than the occupation of the child's father (37)

Although in the present study the part played by the variables concerned with circumstances during childhood did not appear important, it is possible that the biological variables used largely reflected these circumstances, as pointed out by many earlier authors (79 143 144)

The mother's school attendance is often considered a measure of the mother's circumstances during childhood and adolescence. Low birth weight rate has been found to be higher for infants of mothers with less school attendance (12 70). In the present study mother's school attendance was a discriminant moderately increasing the risk only in the analysis of perinatal deaths of infants with birth weights of 2500 g or more. In the parallel analyses of low birth weight infants, in which the number of variables was smaller, the variable *intellectual interest in housekeeping and care of health* acquires, however, a moderate weighting.

The mother's *subjective attitudes* to the desirability of the pregnancy and her views concerning her own frame of mind during pregnancy played no part in the present study either for birth weight or perinatal mortality. Gunter found that psychosomatic and neuropsychiatric traits were more frequent in mothers giving birth to low birth weight infants (63) while according to Davids and De Vault anxiety was correlated with perinatal mortality and low birth weight (33). Abernathy et al. came to the conclusion that psychosomatic symptoms in the mother did not affect the infant's birth weight (1).

Owing to the prospective character of the study all the smokers who used to smoke daily before the pregnancy started were combined in one group. In the analyses concerned with low birth weight infants, smoking increased the risk whereas in the analyses of infants with birth weights of 2500

g or more smoking discriminated rather towards the control group. Table 24 reveals that total perinatal mortality rates were identical for smokers and non-smokers, and reviewed by weight classes the mortality rates of smoking mothers' infants were lower. The increased low birth weight rates equalizing the mortality rates.

Many earlier authors have reported that the birth weights of smokers' infants were significantly lower than those of non-smokers (1 19 46 65 74 85 104 120 121 151 170, 173). The differences in birth weights between smokers and non-smokers' infants fluctuated by an average of 120–229 grams (1 65 74 173). According to Abernathy et al., however, smoking determines only 1.6 per cent of the birth weight variance (1). Smoking has not been found to affect the gestational length (1 85 170).

The results reported from studies of the effect of smoking on perinatal mortality are different. According to the prospective study by Frazier et al. smoking did not affect neonatal mortality while smokers had a significantly higher stillbirth rate (46). Underwood et al. found that the stillbirth rate among smokers showed no significant increase (151). Jarvinen and Osterlund found that smoking did not affect perinatal mortality (74) and Yerushalmy reported in his prospective study that the survival rate of low birth weight infants of smoking mothers was statistically significantly higher than that of non-smokers (170). In British studies, on the other hand, smoking definitely increased mortality (19 120).

The amount of work performed by the mother did not in the present study increase the risk of low birth weight or perinatal mortality. The finding was the same irrespective of whether the mother worked at home or had gainful employment. Stewart assumed that gainful employment together with housekeeping chores increased the low birth weight rate (139) but no other authors report any effect of mother's gainful employ-

The variable distance from population centres increased the risk in all analyses if it was small, and thus supports the above hypothesis of adverse factors connected with urban life. This variable also brings out such a factor in the analysis of perinatal deaths, in which many variables emphasize the risk increasing aspect of large distances.

Two of the distance standards measure the distance from medical care centres. The distance from an antenatal clinic was of no importance in any of the analyses, which suggests that the network of antenatal clinics is sufficiently dense. But the distance from medical officer tends to increase the risk in all analyses. Physicians usually live in major centres of population, and therefore this variable, besides measuring the distance of medical care unit, also measures other developmental levels. In a health survey carried out in Finland (114) the number of diseased people was found to increase as distance from the nearest physician grew. The same study revealed that people living at a distance from any physician had incomes below the average and more often lived in communities with fewer medical officers per head of population. The cumulative effect of various adverse factors, typical of underdeveloped regions, also manifests itself in this way (99).

■ Total results of the discriminant function analyses

The discriminant function analyses which were carried out did not reveal particularly many new features concerning the individual variables. The study showed that in multivariable analysis the effect of the individual variables remains roughly the same as can be expected from studies by the conventional statistical methods.

However the method of analysis used revealed more distinctly than other methods the fact that mothers of low birth weight infants can be better distinguished from those of controls by means of a battery of variables composed of biological and socio-economic

criteria than mothers of infants with birth weights of 2500 g or more that died. It may be assumed that if additional, purely medical variables were used, this difference would either be reduced or the group of infants with birth weights of 2500 g or more could be more readily separated.

Multivariable analysis also reveals the importance of the various factors within the combination of variables used. Perinatal deaths of low birth weight infants were distinguished more emphatically by poverty factors and those of infants with birth weights of 2500 g or more by factors associated with the mother's parents than other groups. The urban way of life seemed to increase the risk in low birth weight infants as a group more than in others.

Multivariable analysis also opens new perspectives for the study of the characteristics of infants assigned to particular risk groups. Combination of the effect of several factors, for example, makes more clearly manifest an abnormal intrauterine growth rate in various groups of mothers. Many other questions concerning the newborn baby may be illuminated in this way when the group studied need not originally be defined on the basis of the child's characteristics. A typical question of this type is the extent to which the factors producing low birth weight also produce an unbalanced conception of female infants. This question is difficult to answer if the groups are separated by birth weight, since girls have lower birth weights. Similarly it may be assumed that additional information can be obtained on other biological or pathophysiological aspects concerning the infant and believed to be associated with intrauterine conditions.

The result of the discriminant function analyses is also of practical significance, especially for babies of low birth weight. The identifiable high risk group covers about 40 per cent of all low birth weight infants although the group is only just under 14 per cent of all the cases. When the total population

in analysis A the risk of low birth weight is increased by internal migration. The weighting for the variable in this analysis is however smaller and when this 43 variable analysis is compared with the 27-variable analysis A 1 the weighting in the different combination of variables is further reduced and has a reverse effect.

In Illsley's study internal migration was correlated with a lower low birth weight rate, but the study was mainly concerned with migration from one city to another (70). As can be seen from Table 22 only 8.5 per cent of the present migrants had been urban dwellers before.

Internal migration that is to say change of place of residence, is connected with many other sociological phenomena in the first place occupational mobility. It is therefore also associated with vertical social mobility. Internal migrants contain various groups, and the motivation for change of place of residence varies from group to group (e.g. unemployed domestic help etc. versus professions with high educational standards) (70).

Internal migration often has national characteristics. In Finland for example, women migrate more frequently than men but this is not a universal feature (153). The predominance of women among migrants has been attributed to the relatively great economic and social independence of women in these communities (95). Some studies of internal migration suggest that the migrants differed favourably in the characteristics measured (school progress, intelligence tests) from the non migrants (70, 153). The correlation recorded in the present study between internal migration and low mortality rates may be linked with the biological and social characteristics of the migrants on the basis of which they made better mothers. Another pattern of explanation is that, while moving about, these persons acquired more information on family planning, medical care, and other factors tending to reduce mortality.

The finding that internal migration is

associated with lower mortality while the low birth weight rate is identical to that among the non-migrants and that in a certain combination of variables internal migration is a risk increasing factor is of considerable interest. It may be associated with the constancy of the low birth weight rates in other words the fact that the tendency to low birth weights is not easy to correct, a recognized and difficult problem (13, 29, 158).

The identical low birth weight rates among migrants and non migrants do not necessarily mean that the causative factors resulting in low birth weight infants also were identical. The low birth weights of some infants may be attributed to purely medical reasons, and be removable by medical means. In those groups with higher total mortality rates, the groups of non migrants, these reasons may be assumed to be the most important.

According to this hypothesis, there should be other factors contributing towards the low birth weight among internal migrants. In Finland internal migration is largely migration from a rural to an urban environment. Raiha has emphasized in many contexts that low birth weight rates are lower in rural districts, provided conditions are otherwise similar (122-124). A similar finding was made in a study based on extensive statistical information (157) according to which the mean birth weight of infants in the United States was significantly higher in rural than urban areas, while the low birth weight rates were lower. The same finding was made when large metropolises were compared with non metropolises and the metropolitan counties with non metropolitan counties the mean birth weights in the latter were higher than in the former (157). In this study the different parity distributions in the regions compared largely accounted for the differences recorded (157). Other factors associated with the urban way of life which increase the low birth weight risk await detailed investigation but the rural way of life may be assumed to be physically healthier.

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Multi variable analysis also opens new perspectives for the study of the characteristics of infants assigned to particular risk groups. Combination of the effect of several factors, for example, makes more clearly manifest an abnormal intrauterine growth rate in various groups of mothers. Many other questions concerning the newborn baby may be illuminated in this way when the group studied need not originally be defined on the basis of the child's characteristics. A typical question of this type is the extent to which the factors producing low birth weight also produce an unbalanced conception of female infants. This question is difficult to answer if the groups are separated by birth weight, since girls have lower birth weights. Similarly it may be assumed that additional information can be obtained on other biological or pathophysiological aspects concerning the infant and believed to be associated with intrauterine conditions.

The result of the discriminant function analyses is also of practical significance, especially for babies of low birth weight. The identifiable high risk group covers about 40 per cent of all low birth weight infants although the group is only just under 14 per cent of all the cases. When the total population

of mothers involved advance identification of such a high proportion of low birth weight infants is a remarkable result. The low birth weight rate of 12.5 per cent of the identifiable high risk group differs markedly from the rate for the remaining group which is 2.8 per cent. The difference between mortality rates, 51.4 per thousand and 19.3 per thousand, also stands out. The mean birth weight of the non low birth weight infants assigned to the high risk group was also lower than in the low risk group. Higher mortality rates have been found to be connected with the lower birth weights. Survivals may be assumed to represent different levels which can be measured by varying degrees of health for example by mortality rates after the perinatal period e.g. during infancy and later childhood. Were this assumption accepted the health of the infants of the high risk group with birth weights of 2500 g or more and living at the end of the perinatal period would be poorer and the later mortality rates during childhood higher than those of the infants assigned to the low risk group. These cases would represent an above-average level of health in the high risk group yet an increased risk which should be recognized. Detailed investigation of these aspects must, however be postponed to the second continuation section of the present study project.

Discriminant function analysis might be useful in practical health care in antenatal clinics. As can be seen from the study of the parallel analyses (p. 34) the number of variables required to achieve a discriminant function of the same order of magnitude is considerably smaller than that used in the present study. On the basis of the results, a battery of 20 of the best variables would be adequate for practical purposes. The best discriminant variables, moreover are based on simple and practical questions which the mothers can easily answer. Classification of one case by computer on the basis of a ready made discriminant function of 20 variables

costs mk 1.50 (36 USA cents). This price can be compared with the price of mk 7.0 laboratories charge for blood group determination, or alternatively for an Rh antibody test. As the mothers would manage the completion of the questionnaire largely on their own the mailing and other administrative work to be done by the medical personnel in risk group classification would roughly equal that in blood sampling.

An essential difference in this comparison is of course that the information supplied by blood group and Rh antibody tests leads to specific treatment, depending on the information obtained. Identification of high risk groups aims at intensified antenatal care and adequate obstetric treatment, although their specificity or potential therapy on many points is not yet comparable e.g. with the management of blood group immunizations.

On the other hand many of the factors in question i.e. discriminant variables, may be known without the help of a computer. This is partly true, but one-third of the series are, for example, primiparas, one-fifth are smokers, and over 8 per cent have previous low birth weight infants — hence the various individual variables make the identifiable risk group so large that adequate care cannot be provided from the medical care resources available.

It is essential to continue the analyses by complementing the variables with important medical data obtainable at the beginning of pregnancy such as toxæmia, blood group immunizations and maternal diabetes. By this means it is possible to estimate the total capacity of discriminant function analyses for identification of high risk groups in the earliest phase of pregnancy.

Probability classification by discriminant function analysis is particularly useful for practical work in regions with few physicians and long distances, but with a sufficient net work of antenatal clinics and high educational level of the population. In a region of this type antenatal clinic work could be very much

intensified for the high risk cases by means of a classification programme derived from the results of the present study

Knowledge of how good results might be obtainable in the prophylaxis of low birth weight infants is far from complete. There is a need for simultaneous research into, and intensive work for early identification of high risk cases at the beginning of pregnancy

thorough medical examination of the elicited high risk cases, and intensified obstetric and pediatric care.

Low birth weight rate is also a considerable economic issue. Prophylaxis is much less expensive than the provision of care for low birth weight infants (96) not to mention the fact that not all problems associated with the subject are measurable in terms of money

of mothers is involved advance identification of such a high proportion of low birth weight infants is a remarkable result. The low birth weight rate of 12.5 per cent of the identifiable high risk group differs markedly from the rate for the remaining group which is 2.8 per cent. The difference between mortality rates, 51.4 per thousand and 19.3 per thousand, also stands out. The mean birth weight of the non low birth weight infants assigned to the high risk group was also lower than in the low risk group. Higher mortality rates have been found to be connected with the lower birth weights. Survivals may be assumed to represent different levels which can be measured by varying degrees of health for example by mortality rates after the perinatal period, e.g. during infancy and later childhood. Were this assumption accepted, the health of the infants of the high risk group with birth weights of 2500 g or more and living at the end of the perinatal period would be poorer and the later mortality rates during childhood higher than those of the infants assigned to the low risk group. These cases would represent an above-average level of health in the high risk group yet an increased risk which should be recognized. Detailed investigation of these aspects must, however be postponed to the second, continuation section of the present study project.

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hazmaton separated all infants with birth weight of less than 2500 g as a group.

All the groups used in discriminant function analyses were formed by probability classification based on the discriminant function of each analysis. The total number of cases in the study was classified by the probability classification based on the discriminant function analysis of all infants with birth weights under 2500 g. The characteristics of the mothers and infants of the risk groups identifiable by this method were calculated. With increasing probability of risk, the mean birth weight and mean length at birth decrease, while mortality rate and the rate of infants with birth weight under 2500 g increase sharply. The combined perinatal mortality rate of the high risk groups was 51.4 per thousand and the frequency of birth weight under 2500 g was 12.5 per cent while

for the remaining low risk group the figures were 19.3 per thousand and 2.8 per cent, respectively. The high risk group contained 41 per cent of all infants with birth weight under 2500 g and corresponded to roughly 14 per cent of all the cases in the series.

The lower mean birth weight of the infants of high risk groups is distinctly apparent as early as in the 29th to 30th weeks of gestation. The gestational phases according to which various differences in intrauterine growth were demonstrable, and the use of multivariable analyses to trace these differences, were discussed.

In conclusion, the value of probability classification on the basis of the results of discriminant function analysis for early identification of risk group in practical antenatal clinic work was considered.

Summary

The study covered 11 905 (11 931) single births in North Finland during one year (1966) which was approximately 96 per cent of all births in the region during this period.

Variations in birth weight and gestational length were presented and intrauterine growth curves by percentile values calculated.

The mortality rate calculated per weight group was lowest for the weight range of 3500—3999 grams and in the 40th week of gestation. On the intrauterine growth curves, the mortality rate was lowest from the 50th to the 90th percentiles, double the lowest rate between the 10th and 50th percentiles, and ten times the lowest rate in the area under the 10th percentile. Above the 90th percentile the mortality rate was slightly higher than for the 50—90 percentile range in pre-term but not in full term births. A special study was made of the effect of inclusion or exclusion of macerated stillbirths in a comparison of this type.

The correlations of the maternal biological characteristics and socio-economic circumstances with low birth weight rates and perinatal mortality rates were calculated and the possibility of predicting the latter on the basis of the former was estimated. These calculations were carried out by discriminant function analysis. The groups to be separated by analysis were 1000 control cases (birth weight 2500 g or more, living at the end of perinatal period and gestational age 38—42 weeks, in cases where it was known) taken by random sampling from among some 10 000 cases, and in the different analyses one each of the following groups: (a) birth weight less than 2500 g, survivals and deaths, 499 cases, (b) birth weight less than 2500 g, deaths, 164

cases, and (c) birth weight 2500 g or more, deaths, 119 cases.

The variables in the discriminant function analysis were maternal characteristics, of which none had anything to do with the course of pregnancy, delivery or the infant born. A total of 47 variables were used and as far as they were concerned the study was prospective. According to their contents, the variables belonged to the following groups: biological characteristics, social status, conditions during childhood, school attendance and intellectual interest, attitudes, smoking, working housing level, standard of living, internal migration and character of the current and earlier places of residence.

Parallel analyses, with a number of different variables, were carried out on the groups with weights less than 2500 g. The purpose was to illustrate the effect of a different combination and number of variables.

In all the analyses in which infants weighing less than 2500 g at birth were the group to be separated, the discriminant function was statistically highly significant, and in the analysis concerned with perinatal deaths of infants weighing 2500 g or more at birth it was statistically significant.

In all analyses the maternal biological characteristics were the essential discriminant factors. Poverty factors were better discriminants for the perinatal deaths of infants with birth weights under 2500 g than others, while factors associated with the mother's parents discriminated the perinatal deaths of infants with birth weight of 2500 g or more. All perinatal deaths were distinguished by regional underdevelopment and lack of internal migration, while factors associated with ur-

baseline separated all infants with birth weight of less than 2500 g as a group.

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Manchester January 1969

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Appendix 1

Variables used in discriminant function analyses

The question concerning the variable in interview form	Range of values for each variable and explanations
Year of birth	<p>1 <i>Mother's age</i> The last 2 digits of year of birth. (18—32)</p>
Mother's height (without shoes) cm measured not known	<p>2 <i>Mother's height</i> The last 2 digits of height. (40—76)</p>
Mother weight before pregnancy Not known Weight at first antenatal clinic visit month of gestation.	<p>3 <i>Mother weight</i> kg Kilograms. (13—107) kg in Where weight before pregnancy was not known the weight of the first antenatal clinic visit was used if obtained before the 4th month of gestation.</p>
Mother age at the beginning of first menstrual period years	<p>4 <i>Menarche age</i> Age, years. (10—25)</p>
Para	<p>5 <i>Mother parity</i> Number of pregnancies excluding abortions and including the present one. (1—16)</p>
How many abortions?	<p>6 <i>Number of abortions</i> Number of abortions divided by the sum of pregnancies carried to term plus abortions.</p>
Number of infants with birth weights under 2500 g not known	<p>7 <i>Presents low birth weight infants</i> Number divided by variable 5.</p>
Have any children died under four weeks of age? Yes No If yes, how many	<p>8 <i>Presents perinatal mortality</i> Number divided by variable 3.</p>
Maternal status Married 1 Unmarried, widow or divorced 2	<p>9 <i>Mother marital status</i> Directly from the reply (1—2)</p>
Mother occupation	<p>10 <i>Mother's occupation</i> 0 = at home, not trained for any occupation. Occupations were classified I—IV according to their social evaluation. Farmer wife was given the value 2 if land under plough equalled more than 3 hect. area, and 3 if the area was smaller (0—4)</p>

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21 Mother' school attendance

No school or ambulatory school	0	Directly from reply (0-8)
1-4 years of primary school	1	
5-8 years of primary school or unfinished secondary school	2	
4-2 years of vocational school	3	
Over 2 years of vocational school	4	
5 years of secondary school	5	
More than 5 years of secondary school	6	
Miscellaneous	7	
Miscellaneous and more	8	

22. Intellectual interest in housekeeping and care of health

Does the mother learn about housekeeping, children's care or public health facilities from press, radio or television?	Directly from reply (1-5)
Regularly	1
Fairly often	2
Sometimes	3
Seldom	4
Never	5

23 Desirability of the pregnancy

The mother finds this pregnancy	Directly from reply (1-3)
accurred at propitious time	1
would have been more desirable later	2
would not have occurred at all	3

24 Mother' frame of mind during pregnancy

Has mother frame of mind during this pregnancy been	Directly from reply (1-3)
normal	1
depressed	2
very depressed	3

25 Mother' attitude toward support by public authorities

Which of the following attitudes does the mother prefer	Directly from reply (1-3)
One should make conscious efforts to improve one's own economic standing	1
One had better be happy with the conditions one has	2
Public authorities should give people more help than they do today	3

26 Mother' smoking

Did the mother smoke at least one cigarette or one pipeful day during the 12 months preceding this pregnancy	Directly from reply (0-1)
0 no	
1 yes	

27 Mother' attitude to strenuousness of work

Does the mother consider her occupation (at home or elsewhere)	Directly from reply (1-5)
very strenuous	1
strenuous	2
moderately strenuous	3
relatively easy	4
easy	5

11 Father's occupation

Father's occupation

Occupations were classified I-IV as for variable 10. Farmers with minimum 8 hectares under plough belonged to class 2, others to class 3 (1-4)

12 Is father a farmer?

Information obtained from reply to variable 11 (1-2)

1 no 2 yes

13 Mother's sector of economy

- 0 No occupation or not working in the occupation Directly from reply (0-4)
 1 Agriculture forestry fishing
 2 Commerce
 3 Services (to community sector of economy private persons)
 4 Industries, building, communications
 Not known

14 Father's sector of economy

- 0 No occupation Directly from reply (0-6)
 1 Agriculture, forestry fishing
 2 Industries (incl. electricity gas, water) crafts
 3 Building
 4 Commerce
 5 Communications
 6 Services (to community sector of economy private persons)
 Not known

15 Mother's vocational standing

- 0 No occupation, or not working in the occupation Directly from reply (0-4)
 1 Employee self-employed
 2 Manager official
 3 Worker
 4 Assisting family member
 Not known

16 Father's vocational standing

- 1 Employer self-employed Directly from reply (1-5)
 2 Manager official
 3 Worker
 4 Assisting family member
 5 No occupation
 Not known

17 Occupation of mother's father

Occupation of mother's father (when mother was 15 years old) The variable obtained is also as under variable 11 except that all farmers were combined with value 3 (1-4)

18 Was mother's father a farmer?

Information obtained from reply to variable 17 (1-2)
 1 no 2 yes

19 Number of mother's siblings

Number of mother's sisters and brothers (living and dead) Number except that any number exceeding 8 is entered as 8 (0-8)

20 Number of mother's dead siblings

How many of mother's siblings died before the age of 15 Number of dead siblings died before the age of 15

21 Mother school attendance

No school or ambulatory school	0	Directly from reply (0-8)
1-4 years of primary school	1	
5-8 years of primary school or unfinished secondary school	2	
1 1/2-2 years of vocational school	3	
Over 2 years of vocational school	4	
5 years of secondary school	5	
More than 5 years of secondary school	6	
Matriculation	7	
Matriculation and more	8	

22 Intellectual interest in housekeeping and care of health

Does the mother learn about housekeeping, children's care or public health facilities from press, radio or television? Directly from reply (1-5)

Regularly	1
Fairly often	2
Sometimes	3
Seldom	4
Never	5

23 Desirability of the pregnancy

The mother finds that this pregnancy occurred at propitious time	1	Directly from reply (1-3)
would have been more desirable later	2	
should not have occurred at all	3	

24 Mother's frame of mind during pregnancy

Has mother frame of mind during this pregnancy been		Directly from reply (1-3)
as usual	1	
depressed	2	
very depressed	3	

25 Mother attitude towards support by public authorities

Which of the following alternatives does the mother prefer		Directly from reply (1-3)
One should make continuous efforts to improve one's own economic standing	1	
One had better be happy with the conditions one lives in	2	
Public authorities should give people more help than they do today	3	

26 Mother smoking

Did the mother smoke at least one cigarette or one pipeful day during the 12 months preceding this pregnancy		Directly from reply (0-1)
0 no		
1 yes		

27 Mother attitude to strenuousness of work

Does the mother consider her occupation (= daily work home and/or elsewhere)		Directly from reply (1-5)
very strenuous	1	
strenuous	2	
moderately strenuous	3	
relatively easy	4	
easy	5	

11 Father's occupation

Father's occupation

Occupations were classified I-IV as for variable 10. Farmers with minimum 8 hectares under plough belonged to class 2, others to class 3 (1-4)

12 Is father a farmer?

Information obtained from reply to variable 11 (1-2)
1 no 2 yes

13 Mother's sector of economy

- 0 No occupation, or not working in the occupation Directly from reply (0-4)
- 1 Agriculture, forestry fishing
- 2 Commerce
- 3 Services (to community sector of economy private persons)
- 4 Industry, building, communications
- Not known

14 Father's sector of economy

- 0 No occupation Directly from reply (0-6)
- 1 Agriculture, forestry fishing
- 2 Industries (incl. electricity gas, water), crafts
- 3 Building
- 4 Commerce
- 5 Communications
- 6 Services (to community sector of economy private persons)
- Not known

15 Mother's vocational standing

- 0 No occupation, or not working in the occupation Directly from reply (0-4)
- 1 Employer self-employed
- 2 Manager official
- 3 Worker
- 4 Assisting family member
- Not known

16 Father's vocational standing

- 1 Employer self-employed Directly from reply (1-5)
- 2 Manager official
- 3 Worker
- 4 Assisting family member
- 5 No occupation
- Not known

17 Occupation of mother's father

Occupation of mother's father (when mother was 15 years old) The variable obtained its values as under variable 11 except that all farmers were combined, with value 3 (1-4)

18 Was mother's father a farmer?

Information obtained from reply to variable 17 (1-2)
1 no 2 yes

19 Number of mother's siblings

Number of mother's sisters and brothers (living and dead) Number except that any number exceeding 8 is entered as 9 (0-8)

20 Number of mother's dead siblings

How many of mother's siblings died before the age of 15? Number of dead siblings divided by total number of siblings.

21 Mother' school attendance

No school or ambulatory school	0	Directly from reply (0-8)
1-4 years of primary school	1	
5-8 years of primary school or unfinished secondary school	2	
9-12 years of primary school	3	
Over 2 years of vocational school	4	
5 years of secondary school	5	
More than 5 years of secondary school	6	
Matriculation	7	
Matriculation and more	8	

22 Intellectual interest in housekeeping and care of health

Does the mother learn about housekeeping, children care or public health facilities from press, radio or television?		Directly from reply (1-5)
Regularly	1	
Fairly often	2	
Sometimes	3	
Seldom	4	
Never	5	

23 Desirability of the pregnancy

The mother finds that this pregnancy occurred at propitious time	1	Directly from reply (1-3)
would be been more desirable later	2	
should not have occurred at all	3	

24 Mother' frame of mind during pregnancy

Has mother's frame of mind during the pregnancy been		Directly from reply (1-3)
as usual	1	
depressed	2	
very depressed	3	

25 Mother attitude towards support by public authorities

Which of the following attitudes on does the mother prefer		Directly from reply (1-3)
One should make considerable efforts to improve one's own economic standing	1	
One had better be happy with the conditions one lives in	2	
Public authorities should give people more help than they do today	3	

26 Mother' smoking

Did the mother smoke at least one cigarette or one pipeful day during the 12 months preceding this pregnancy?		Directly from reply (0-1)
0 no		
1 yes		

27 Mother attitude to strenuousness of work

Does the mother consider her occupation (= daily work at home and/or elsewhere)		Directly from reply (1-5)
very strenuous	1	
strenuous	2	
moderately strenuous	3	
rather easy	4	
easy	5	

28 *Mother's gainful employment*

Has the mother been gainfully employed outside her home during this pregnancy? Directly from reply (1-3)

no	1
mainly half time	2
full time	3

29 *Mother's post re at work*

Does the mother in her present occupation (= daily work at home and/or elsewhere) mainly Directly from reply (1-3)

sit	1
stand	2
move about	3

30 *Does the mother work indoors or outdoors?*

Does the mother work in her occupation Directly from reply (1-3)

mainly indoors	1
mainly outdoors	2
indoors and outdoors equally	3

31 *Help in housekeeping*

Has the mother during pregnancy had in house keep g Directly from reply (1-3)

paid help	1
help by family members	2
no help	3

32 *Size of household*

How many persons are there in the household? Number of persons except that any number exceeding 9 is entered as 9 (1-9)

persons

33 *Number of persons under 15 years of age*

(Preceding question continued) How many of them are under 15 years of age? Number of children except that any number exceeding 8 is entered as 8 (0-8)

persons

34 *Number of rooms in family dwelling*

How many rooms does the household occupy including kitchen (but excluding kitchenette, recess for beds, bathroom laundry and any sub-let rooms)? Number of rooms except that any number exceeding 9 is entered as 9 (1-9)

rooms

35 *Electricity*

Is the family dwelling equipped with electricity? Directly from reply (1-2)

1 yes 2 no

36 *Running water*

Is the family dwelling equipped with running water? Directly from reply (1-2)

1 yes 2 no

37 *House ownership*

Does the family own a flat or a house? Directly from reply (1-2)

1 yes 2 no

38 *TV set*

Television set in the family dwelling? Directly from reply (1-2)

1 yes 2 no

39 *Ownership of car*

Does the family own a car? Directly from reply (1-2)

1 yes 2 no

40 Degree of industrialization of community

Place of residence

Developmental score calculated from 18 indicators (106) (See page 51) (1.7-9.3)

41 Nature of place of residence

Family lives in

Directly from reply (1-3)

- | | |
|---|---|
| town | 1 |
| large village or other centre of population | 2 |
| remote village | 3 |

42 Internal migration

Has the member also lived in the same village or town?

Directly from reply (1-2)

- | | | | |
|-----|---|----|---|
| Yes | 1 | No | 2 |
|-----|---|----|---|

43 Nature of other place of residence

(Preceding question continued)

Directly from reply (0-3)

If not, was her place of residence prior to the age of 15 usually

- | | |
|---|---|
| town | 1 |
| large village or other centre of population | 2 |
| remote village | 3 |

No internal migration

0

44 Distance from maternal birth

1 less than 300 m

1

Directly from reply (1-9)

2 0.3-2.9 km

2

3 3.0-9.9 km

3

4 10.0-16.9 km

4

5 17.0-23.9 km

5

6 24.0-30.9 km

6

7 31.0-100.0 km

7

8 101-200 km

8

9 201 km or more

9

not known

45 Distance from neighbour

Distance from family dwelling to the nearest neighbour (same classification as for Variable 44)

Directly from reply (1-9)

46 Distance from centre of population

Distance from family dwelling to nearest large village or similar (same classification as for Variable 44)

Directly from reply (1-9)

47 Distance from medical officer

Distance from family dwelling to the nearest physican surgery (same classification as for Variable 44)

Directly from reply (1-9)

28 *Mother's gainful employment*

Has the mother been gainfully employed outside her home during this pregnancy? Directly from reply (1—3)

no	1
mainly half time	2
full time	3

29 *Mother's posture at work*

Does the mother in her present occupation (= daily work at home and/or elsewhere) mainly Directly from reply (1—3)

sit	1
stand	2
move about	3

30 *Does the mother work indoors or outdoors?*

Does the mother work in her occupation Directly from reply (1—3)

mainly indoors	1
mainly outdoors	2
indoors and outdoors equally	3

31 *Help in housekeeping*

Has the mother during pregnancy had in house keeping Directly from reply (1—3)

paid help	1
help by family members	2
no help	3

32 *Size of household*

How many persons are there in the household? Number of persons except that any number exceeding 9 is entered as 9 (1—9)

persons	
---------	--

33 *Number of persons under 15 years of age*

(Preceding question continued) How many of them are under 15 years of age? Number of children except that any number exceeding 8 is entered as 8 (0—8)

persons	
---------	--

34 *Number of rooms in family dwelling*

How many rooms does the household occupy including kitchen (but excluding kitchenette, recess for beds, bathroom, lavatory and any sub-let rooms)? Number of rooms except that any number exceeding 9 is entered as 9 (1—9)

rooms	
-------	--

35 *Electricity*

Is the family dwelling equipped with electricity? Directly from reply (1—2)

1 yes	2 no
-------	------

36 *Running water*

Is the family dwelling equipped with running water? Directly from reply (1—2)

1 yes	2 no
-------	------

37 *House ownership*

Does the family own a flat or house? Directly from reply (1—2)

1 yes	2 no
-------	------

38 *TV set*

Television set in the family dwelling? Directly from reply (1—2)

1 yes	2 no
-------	------

39 *Ownership of car*

Does the family own a car? Directly from reply (1—2)

1 yes	2 no
-------	------

Appendix 3

[illegible]

TABLE 28 Distribution of perinatal deaths by birth weight and by gestational age Perinatal mortality rates per thousand by 100 gram weight groups and by gestational weeks calculated from the figures on the total number of cases given in Table 27

Appendix 2

[illegible]

TABLE 27 Distribution of the total number of cases by birth weight and by gestational age

ACTA
PÆDIATRICA
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SUPPLEMENT 192-1969

SURVEILLANCE OF ACUTE VIRAL
RESPIRATORY DISEASES IN CHILDREN

SYLVEA VIKMA

ALMQVIST & WIKSTEDT STOCKHOLM, SWEDEN

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Printed by Almqvist & Wiksells Boktryckeri AB Uppsala

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DISEASES IN CHILDREN**

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 192, 1969

*Department of Virology and Children's Hospital, University of Turku
Turku, Finland*

SURVEILLANCE OF ACUTE VIRAL
RESPIRATORY DISEASES IN
CHILDREN

by

Leena Vihma

TURKU 1969

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Printed in Finland

KIRJAPAINO POLYTYPOS TURKU 1969

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Introduction

The acute respiratory infections, as the most common illnesses of man, are of interest to clinicians, epidemiologists and microbiologists. Interest in the respiratory illnesses of adult persons is to some extent due to their great importance as causes of absenteeism, which results in economic loss. These illnesses may lead to complications in patients suffering from other chronic disease and may even be fatal in old patients.

Pediatricians and virologists are concerned with the acute respiratory illnesses of children for somewhat other reasons. The severity of these illnesses, especially in young infants, often directly necessitates the existence of adequate hospital wards and the availability of immediate medical aid. Because of the commonness of acute respiratory diseases in children, the problem of secondary infections is considerable.

Research concerning acute respiratory illness has been extensive and study groups have approached the problem of acute respiratory infections in children in different ways. The patients in children's hospitals and out-patient clinics in many countries have been

carefully studied. The respiratory cases in children have been recorded in several long-term family studies, most of these studies have not been directly concerned with respiratory illnesses of children. In well defined groups of children, e.g. in residential nurseries and in children's homes, the acute respiratory infections have been studied both during epidemics and for longer periods. Even children in some general and pediatric practices have been studied for acute respiratory infections, sometimes concurrently with a hospital series. However no simultaneous studies of respiratory infections both in children living in their normal home environment and in children living in institutions have been reported.

In this study the significance of common viral agents in the etiology of acute respiratory infections in children was evaluated by surveying a group of families and a group of children in a residential nursery. The usefulness of a group of institutionalized children as an index of respiratory disease in the children of the whole community was evaluated.

agc agents in lower respiratory tract disease (7-34) and in febrile cases of upper respiratory infection (19). The croup syndrome is often associated with parainfluenza virus, particularly type 1 infection (1). Chanock and Parrott (17) estimate that 7 to 18 per cent of all respiratory disease in children is associated with parainfluenza virus infections.

The influenza virus types A and B are sometimes of importance during epidemics, reaching attack rates of 3 to 50 per cent, mainly in children over 5 years old (67). Outbreaks of influenza B virus infection have been described in schools (67). The overall importance of this virus group in the etiology of acute respiratory infections in children is less than that of RS and parainfluenza viruses (17).

Adenoviruses may be associated with all forms of respiratory tract infection (62, 72). Opinions vary on the importance of adenoviruses as a cause of respiratory disease. Chanock *et al.* (17) estimate 8 to 9 per cent of the acute respiratory disease seen in a children's hospital to be due to adenoviruses. Hilleman *et al.* (33) found evidence of adenovirus infection in only 5 per cent of their patients. From data of several studies van der Ven (79) reckoned the importance of adenoviruses to vary from 2.7 to 3 per cent of respiratory illnesses in children; the latter percentage was observed in a hospital series during an adenovirus epidemic in Sweden (64). When the adenovirus types recovered from children with respiratory illnesses were investigated by Vargosko *et al.* (71) the majority were found to belong to types 1, 2, 5 and 7. These types are known to produce febrile upper respiratory tract infections in infants (64).

In Finland, the occurrence of adenovirus infections in children treated at hospital for acute respiratory illnesses were studied by Jansson *et al.* (37). In 14 per cent an association with adenoviruses was observed. Adenovirus epidemics with respiratory symptoms

in children due to types 1 and 2 have been reported by Formell *et al.* (20) and due to type 7 by Jansson *et al.* (38).

Rhinoviruses were found to be associated with 4 to 5 per cent of the respiratory illnesses sampled by Chanock *et al.* (17) and Hilleman (33). About the same proportion of respiratory infections in children were associated with rhinoviruses in the Medical Research Council's collaborative study in Britain (47).

The respiratory illnesses caused by *M. pneumoniae* undergo wide fluctuations in prevalence from year to year (17). In some periods it has been associated with 5 to 10 per cent of the lower respiratory disease in children (17, 43). *M. pneumoniae* is considerably more important as a respiratory pathogen in children over 10 years of age than in infants and young children (28).

FAMILY STUDIES

Several long-term family studies have been programmed in the USA and in Britain, mainly in order to collect information on the occurrence of the common cold. These studies have been reviewed by Tyrrell (69).

In the extensive Cleveland study by Dingle *et al.* (23) virus isolations and serologic tests were performed. During this 10-year study of 55 families, an incidence of 5 to 8 common respiratory illnesses per year was observed in the children. An adenovirus type 3 outbreak was observed in this study population in 1964 and in a serologic study in the same population 4 per cent of the respiratory infections in children could be attributed to the adenovirus infection. Parainfluenza virus type 3 infections were considered to be common among the children. The influenza A2 pandemic of 1967 coincided with the study; the incidence was 73 per cent in the school-children and 30 per cent in the preschool children. In other influenza A and B outbreaks attack rates of 15 to 25 per cent were reported.

Review of the Literature

THE VIRAL ETIOLOGY OF ACUTE RESPIRATORY DISEASE IN CHILDREN

Influenza virus infections have been known since the 1930's to occur in children during influenza epidemics (67). In 1954 Huebner *et al.* (35) were the first to demonstrate the adenovirus etiology in acute respiratory tract infections of children. From 1956 onwards, the parainfluenza viruses were recovered from children, parainfluenza virus types 1 and 3 by Chanock *et al.* (18) and parainfluenza virus type 2 by Chanock (13) and Beale *et al.* (4). The following year Chanock *et al.* (20) reported the recovery of respiratory syncytial virus (RS) also known as COA virus of Morris (51) from infants with respiratory illness.

Viruses belonging to a new group were recovered in 1960 and Kendall *et al.* (40) reported the isolation of these rhinoviruses from boarding-school boys, Hilleman *et al.* (33) from younger children. Other respiratory tract pathogens were found among the enteroviruses. Coxsackie B type 5 was reported to be associated with acute respiratory illnesses of children by Babb *et al.* (2) and Vargosko *et al.* (70). Philipson *et al.* (52) and Rosen *et al.* (58) recovered viruses of the ECHO group from children with respiratory disease. Reovirus type 1 infection in institutionalized children was reported by Rosen (57). In 1960 Chanock *et al.* (15) found serologic evidence in children of respiratory tract infection with the Eaton agent (*Mycoplasma pneumoniae*).

Since the publication of these findings, much attention has been given to investiga-

tions of acute respiratory infections in children. Summarizing the available information, Chanock (17), Stuart-Harris (67) and Tyrrell (69) have presented estimates of the importance of a number of viruses in acute respiratory diseases of infancy and childhood.

Each of the pathogenic viruses of the respiratory tract can provoke illnesses ranging from inapparent to severe infections, but obviously some of these viruses are more often responsible than others for severe lower respiratory tract involvement (17, 67, 69).

The RS virus is considered to be the most important viral pathogen in infants. RS infection was detected in 26 to 30 per cent of bronchiolitic illnesses by Chanock *et al.* (17). RS infections occur in epidemics resulting in high infection rates in closed child communities (67, 69). In the series of Chanock *et al.* (17) RS virus was associated with 9.5 per cent of all pediatric respiratory illnesses studied. Hilleman *et al.* (33) estimated the importance of RS virus in the outpatient and hospital series at 17–25 per cent of the respiratory infections of children.

In Scandinavia Hornsleth (34) has found RS virus to be the etiologic agent in 10 per cent of children with pneumonia. Berglund (7) has reported the same features of RS infection in Finland. The epidemiology of the RS virus was followed by Berglund for 3 years, and 4 outbreaks were observed during this period. The agent was found to spread potently among day-nursery children and within families. In addition RS virus was recovered from the middle ear exudates of 16 children suffering from RS virus infection.

Parainfluenza viruses are important eti-

logic agents in lower respiratory tract disease (17-24) and in febrile cases of upper respiratory infection (19). The croup syndrome is often associated with parainfluenza virus, particularly type 1, infection (17). Chanock and Parrott (17) estimate that 7 to 16 per cent of all respiratory disease in children is associated with parainfluenza virus infections.

The influenza virus types A and B are sometimes of importance during epidemics, reaching attack rates of 25 to 40 per cent, mainly in children over 5 years old (67). Outbreaks of influenza B virus infection have been described in schools (67). The overall importance of this virus group in the etiology of acute respiratory infections in children is less than that of RS and parainfluenza viruses (17).

Adenoviruses may be associated with all forms of respiratory tract infection (62, 79). Opinions vary on the importance of adenoviruses as a cause of respiratory disease. Chanock *et al.* (17) estimate 8 to 9 per cent of the acute respiratory disease seen in a children's hospital may be due to adenoviruses. Hilleman *et al.* (33) found evidence of adenovirus infection in only 5 per cent of their patients. From data of several studies rather Leen (79) reckoned the importance of adenoviruses to vary from 7 to 30 per cent of respiratory illnesses in children; the latter percentage was observed in a hospital series during an adenovirus epidemic in Sweden (64). When the adenovirus types recovered from children with respiratory illnesses were investigated by Vargosko *et al.* (71) the majority were found to belong to types 1, 2, 4 and 7. These types are known to produce febrile upper respiratory tract infections in infants (62).

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The respiratory illnesses caused by *M. pneumoniae* undergo wide fluctuations in prevalence from year to year (17). In some periods it has been associated with 0 to 10 per cent of the lower respiratory disease in children (17-48). *M. pneumoniae* is considerably more important as a respiratory pathogen in children over 10 years of age than in infants and young children (28).

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The Virus Watch program of Fox *et al* (26-63-24) was a continuing surveillance of a group of families, living in metropolitan New York for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study. The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period. In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 6 to 11 per cent in different age groups.

STUDIES IN GROUPS OF INSTITUTIONALIZED CHILDREN

Bell *et al* (5) carried out the first long term clinical and virologic study of nursery children in Washington, D.C. The respiratory illnesses were investigated in this large Junior Village study over a period of 3 years. On average, 50 young children were under observation. The mean weekly total illness rate was 21.6 per cent. Infections with adenovirus types 1, 3 and 5, influenza A2, parainfluenza types 1 and 3 and Coxsackie B type 3 were significantly associated with acute febrile illness. Kapikian *et al* (39) described an RS virus outbreak in Junior Village. Eight outbreaks of parainfluenza virus infections were observed (19).

In a residential nursery for children aged less than 5 years with a mean population of 18, observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year. During the study period of 8 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed. Fifteen children yielded adenoviruses types 1, 2 and 5 but three isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) report a longitudinal survey of the respiratory illnesses in a group of infants 4 months to 2 years of age under treatment for tuberculous. During the 3 years of observation, one epidemic of respiratory disease due to RCHO virus type 7 and one epidemic due to RS virus were detected.

A study of acute respiratory diseases in children's home in Kansas City was performed by Roland *et al* (53). Sixty-one children 2 to 12 years old had an average of 17 illnesses per person year of observation. Twelve well defined outbreaks of illness were associated with influenza virus type B and RCHO virus type 26. A parainfluenza virus type outbreak was observed in the children's home during the fifth year of surveillance in the home (32).

Wiken *et al* (1) observed children under 3½ years of age in a nursery in Edinburgh. Evidence of respiratory illness. During the 6 months of the survey 26 respiratory illnesses were experienced per child. Forty-two percent of 105 illnesses were associated with viral infections. RS and adenovirus infections were observed in 16 cases, parainfluenza type 3 in 15 cases and influenza C infections in 1 case during the survey. Adenovirus infections were distributed evenly throughout the study period. The other infections occurred in well-defined outbreaks, the influenza outbreak occurring twice.

In Finland, Borglund *et al* (8) followed the respiratory infections in a small nursery for 21 months. Two RS virus outbreaks coincided with epidemics involving the whole city. There was evidence that one outbreak probably was associated with influenza A virus, prevalent in the area at the same time. On the average each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation.

Mascoli *et al* (46) investigated 741 throat

specimens taken from respiratory illness cases in nurseries for detection of rhinoviruses and 3.5 per cent of these specimens yielded rhinoviruses in children aged 3 to 5 years.

Numerous reports dealing with isolated outbreaks of acute respiratory illnesses associated with RS virus (41 50 59 66) adenoviruses (73) and enteroviruses (8, 11) in nurseries and other child communities have been published.

Stern *et al.* (66) reported an outbreak of *M. pneumoniae* infection in a home for children. In their surveillance of acute respiratory disease at the children's home in Kansas City Glezen *et al.* (27) included reports on the mycoplasma. One slowly progressing outbreak of *M. pneumoniae* was observed, 27 out of 46 children showing evidence of infection.

The Virus Watch program of Fox *et al* (26 63 24) was a continuing surveillance of a group of families, living in metropolitan New York, for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study. The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period. In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 8 to 11 per cent in different age groups.

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In a residential nursery for children aged less than 5 years with a mean population of 18 observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year. During the study period of 9 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed. Fifteen children yielded adenoviruses types 1 and 2 but these isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) report a longitudinal survey of the respiratory illnesses in a group of infants 4 months to 3 years of age under treatment for tuberculosis. During the 3 years of observation one epidemic of respiratory disease due to FCIO virus type 7 and one epidemic due to RS virus were detected.

A study of acute respiratory diseases in children's home in Kansas City was performed by Poland *et al* (53). Sixty-one children 2 to 12 years old had an average of 2.7 illnesses per person year of observation. The well defined outbreaks of illness were associated with influenza virus type B and FCIO virus type 25. A parainfluenza virus type 4 outbreak was observed in the children's home during the fifth year of surveillance in this home (32).

Altken *et al* (1) observed children under 3½ years of age in a nursery in Edinburgh for evidence of respiratory illness. During the 6 months of the survey 2.6 respiratory illnesses were experienced per child. Forty-two per cent of 105 illnesses were associated with virus infections. RS and adenovirus infections were observed in 16 cases, parainfluenza type 3 in 15 cases and influenza C infections in 18 cases during the survey. Adenovirus infections were distributed evenly throughout the study period. The other infections occurred in well-defined outbreaks, the influenza C outbreak occurring twice.

In Finland Berglund *et al* (8) followed the respiratory infections in a small nursery for 91 months. Two RS virus outbreaks coincided with epidemics involving the whole city. There was evidence that one outbreak probably was associated with influenza A virus, prevalent in the area at the same time. On the average each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation.

Mancoli *et al* (46) investigated 741 throat

specimens taken from respiratory illness cases in nurseries for detection of rhinoviruses and 3.5 per cent of these specimens yielded rhinoviruses in children aged 3 to 5 years.

Numerous reports dealing with isolated outbreaks of acute respiratory illnesses associated with RS virus (41, 50, 59, 66), adenoviruses (73) and enteroviruses (6, 11) in nurseries and other child communities have been published.

Sternet *et al.* (66) reported an outbreak of *M. pneumoniae* infection in a home for children. In their surveillance of acute respiratory disease at the children's home in Kansas City Glesen *et al.* (97) included reports on the mycoplasma. One slowly progressing outbreak of *M. pneumoniae* was observed, 97 out of 46 children showing evidence of infection.

The Virus Watch program of Fox *et al* (26 63 24) was a continuing surveillance of a group of families, living in metropolitan New York for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study. The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period. In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 8 to 11 per cent in different age groups.

STUDIES IN GROUPS OF INSTITUTIONALIZED CHILDREN

Bell *et al* (5) carried out the first long term clinical and virologic study of nursery children in Washington D C. The respiratory illnesses were investigated in this large Junior Village study over a period of 3 years. On average 60 young children were under observation. The mean weekly total illness rate was 21.5 per cent. Infections with adenovirus types 1, 3 and 5, influenza A₂, parainfluenza types 1 and 3, and Coxsackie B type 3 were significantly associated with acute febrile illness. Kapikian *et al* (39) described an RS virus outbreak in Junior Village. Eight outbreaks of parainfluenza virus infections were observed (19).

In a residential nursery for children aged less than 6 years with a mean population of 18 observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year. During the study period of 8 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed. Fifteen children yielded adenoviruses types 1, 2 and 5 but these isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) reported a longitudinal survey of the respiratory illnesses in a group of infants 4 months to 3 years of age under treatment for tuberculosis. During the 3 years of observation one epidemic of respiratory disease due to FCIO virus type 7 and one epidemic due to RS virus were detected.

A study of acute respiratory diseases in a children's home in Kansas City was performed by Roland *et al* (53). Sixty-one children 2 to 12 years old had an average of 2.7 illnesses per person year of observation. Two well defined outbreaks of illness were associated with influenza virus type B and FCIO virus type 2. A parainfluenza virus type 2 outbreak was observed in the children's home during the fifth year of surveillance in this home (32).

Mitken *et al* (1) observed children under 3½ years of age in a nursery in Edinburgh for evidence of respiratory illness. During the 6 months of the survey 20 respiratory illnesses were experienced per child. Forty-two per cent of 105 illnesses were associated with virus infections. RS and adenovirus infections were observed in 10 cases, parainfluenza type 3 in 15 cases and influenza C infections in 18 cases during the survey. Adenovirus infections were distributed evenly throughout the study period. The other infections occurred in well-defined outbreaks, the influenza C outbreak occurring twice.

In Finland Berglund *et al* (8) followed the respiratory infections in a small nursery for 21 months. Two RS virus outbreaks coincided with epidemics involving the whole city. There was evidence that one outbreak probably was associated with influenza A₂ virus, prevalent in the area at the same time. On the average, each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation.

Mascoli *et al* (46) investigated 741 throat

Materials and Methods

STUDY POPULATION

Nursery group

The nursery group consisted on infants in a small private residential nursery in Turku, Finland. In this nursery Berglund *et al.* (8) previously performed a study and described the details of the organization and conditions in the nursery. A school for nurses is situated in the neighborhood and the nursery serves as a training place for the student nurses. The hygienic standards in the nursery are high.

The residential nursery is intended for infants under 7 years old. It has 16 beds, 4 small isolation rooms, 4 large rooms for 4 infants each and one big playroom for the older infants. Usually only healthy infants are admitted, but sometimes infants with congenital malformations are taken into the nursery for social reasons. Many of the infants admitted are brought directly from maternity hospitals and stay until an adoption is organized, on average for 4 months. A small number of the infants are at the nursery owing to the temporary or permanent inability of their families to take care of them. Every newcomer is first placed in an isolation room for one week and if no signs of infection are observed the infant is moved to a large room.

During the present surveillance 57 infants, 24 girls and 34 boys, were resident at the nursery. The mean number of infants was 15.0, the mean weekly number the same and the median 14. Table 1 shows the mean monthly numbers of infants in the study.

When space is available, the nursery serves as a "hotel" for infants. The "hotel infants" stay in the isolation rooms; occasionally the older "hotel infants" are allowed to play in the common playroom if they stay for a long time. During the observation period, 87 "hotel infants" visited the nursery. Three stayed for a long time, the mean duration of stay for the remaining 84 infants was 6 days. These "hotel infants" were not included in the study.

Family group

Selection of families. The goal was to find families with at least three children, the youngest of whom was an infant. These infants were to form a comparison group for the nursery infants. They should all be nursed in their homes. Suitable families were picked from the indexes kept in the children's welfare centers. The health sisters made the first inquiries and if the mother appeared willing the author made a home visit to explain the purpose of the study and the study procedures. The importance of two bleedings in each respiratory illness was stressed. The families were offered free medical consultation and if necessary free laboratory investigations in the Children's Hospital, University of Turku, during the study period.

The first group of families was recruited in September 1965. It consisted of 31 families. Some families were lost and after 6 months of study it was felt, that more families could be observed. In April 1966 a further group of 17 families was included.

Outlines of the Present Study

The significance of viruses as etiologic agents in acute respiratory infections of children was studied. The techniques available adapted to the recovery of four common viral agents, RS parainfluenza, influenza and adenoviruses, restricted the study mainly to the importance of these viruses.

Another purpose of the study was to evaluate a group institutionalized children as an index of the respiratory illnesses among the children of the whole community.

The objectives were approached by a long term surveillance of acute respiratory illnesses

simultaneously in a group of infants in a residential nursery and in a group of families with infants. During the study the occurrence of respiratory illnesses was recorded for epidemiologic purposes. Patients with respiratory symptoms were studied by virus isolation techniques and serologic tests to determine the virus etiology of the acute respiratory illness. For further evaluation of the importance of RS parainfluenza, influenza and adenovirus infections in children the patients were examined and the clinical data reviewed.

Materials and Methods

STUDY POPULATION

Nursery group

The nursery group consisted of infants in a small private residential nursery in Turku, Finland. In this nursery Berglund *et al.* (8) previously performed a study and described the details of the organization and conditions in the nursery. A school for nurses is situated in the neighborhood and the nursery serves as a training place for the student nurses. The hygienic standards in the nursery are high.

The residential nursery is intended for infants under 7 years old. It has 16 beds, 9 small isolation rooms, 4 large rooms for 4 infants each and one big playroom for the older infants. Usually only healthy infants are admitted, but sometimes infants with congenital malformations are taken into the nursery for social reasons. Many of the infants admitted are brought directly from maternity hospitals and stay until an adoption is organized, on average for 4 months. A small number of the infants are at the nursery owing to the temporary or permanent inability of their families to take care of them. Every newborn is first placed in an isolation room for one week and if no signs of infection are observed the infant is moved to a large room.

During the present surveillance 7 infants, 23 girls and 24 boys, were resident at the nursery. The mean number of infants was 15.0 the mean weekly number the same and the median 15. Table 1 shows the mean monthly numbers of infants in the study.

When space is available the nursery serves as a "hotel" for infants. The "hotel infants" stay in the isolation rooms occasionally the older "hotel infants" are allowed to play in the common playroom if they stay for a long time. During the observation period, 87 "hotel infants" visited the nursery. Three stayed for a long time, the mean duration of stay for the remaining 84 infants was 6 days. These "hotel infants" were not included in the study.

Family group

Selection of families. The goal was to find families with at least three children, the youngest of whom was an infant. These infants were to form a comparison group for the nursery infants. They should all be nursed in their homes. Suitable families were picked from the indexes kept in the children's welfare centers. The health sisters made the first inquiries and if the mother appeared willing, the author made a home visit to explain the purpose of the study and the study procedures. The importance of cough bleedings in each respiratory illness was stressed. The families were offered free medical consultation and if necessary laboratory investigations in the Children's Hospital, University of Turku, during the study period.

The first group of families was recruited in September 1961. In consist of 10 families. These families were not sent after 3 months of study it was felt that more families would be observed in April 1962 a further group of 1 families was recruited.

Table 1 *Mean number of participants in the study by month*

	Nursery group		Family group				
	Infant	Infants	Children —6 yrs	School children 7—10 yrs	Children 11— yrs	Parents	
1965 Sept	18	35	29	35	10	63	
Oct.	15	33	29	35	10	62	
Nov	16	34	28	35	10	60	
Dec.	16	33	28	35	10	60	
1966 Jan	17	33	7	34	8	58	
Feb.	16	33	7	34	7	58	
Mar	14	37	31	38	9	63	
Apr	1	34	43	34	16	90	
May	13	3	44	34	16	90	
June	14	41	31	4	13	80	
July	15	36	36	34	10	7	
Aug	13	43	31	1	13	80	
Sept.	14	49	40	30	14	64	
Oct	15	48	40	49	1	83	
Nov	16	47	39	49	1	81	
Dec.	17	4	39	49	11	82	
1967 Jan.	16	45	38	47	10	8	
Feb.	14	43	3	43	10	76	
Mar	13	43	37	43	10	6	
Apr	12	43	3	43	10	76	
May	14	43	37	44	10	77	
June	14	33	37	28		63	
July	14	37	19	40	3	60	
Aug	16	33	37	30	11	67	
mean	15	40	33	40	10	73	

Family population Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles

— **Infants.** All children under 2 years of age at enrolment in September 1965 or April 1966. The total number of infants was 60: 33 girls and 27 boys. The mean number of infants in the study was 40: the weekly mean the same and the median number was 41 infants.

— **Children 2—6 years of age.** All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group. The total number of children in this group was 47: 20 girls and 27 boys. The mean number of children 2—6

years of age in the study was 30:0 the weekly mean the same and the median 32.

— **School-children 7—10 years of age.** All children in elementary schools during the study period up to 10 years old were included in this group. There were 56 children, 31 girls and 24 boys. The mean number of school-children aged 7—10 years in the study was 40:6 the same as the weekly mean the median was 41.

— **Children 11 years old and older.** All the children aged 11 years or more at enrolment were in this group. There were only 19 such children. The mean number of older children in the study was 10:5 the weekly mean the same and the median 10 children.

The mean number of parents in the study was 72:7 the mean weekly number 72:9 and the median 76.

The mean monthly numbers of persons on observation in each of these age groups is shown in Table 1.

There is a decline in the mean monthly number of participants during the summer months due to loss of children and families on observation during their vacations. Seven families dropped out of the study 4 months because they moved out of town after participation for on average one year three (two of them in the beginning of the study 3 months after 9 months) because of the laborious study procedures. Three families did not want to cooperate because of the bleedings and were released after being in the study for 4, 9 and 1 month. One infant entered a day-nursery and the family was released after 16 months participation in the study. Two persons in the oldest child group were released: one was sent to a tuberculosis sanatorium, the other left home to study elsewhere.

Description of the population

1. The mean and the median age of each study group was calculated at the beginning, middle and end of the study. The results are shown in Table 2. In the nursery group the standard deviations of the mean ages were

5½, 8½ and 7½ months, respectively. On these occasions the youngest infants were 2 months of age, and at the end of the study the oldest infant was 7 years 7 months old.

In the family infants the standard deviations of the mean ages were 5½, 7½ and 9½ months, respectively. In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged 2–6 years, the age range was from 2 to 6 years, from 3 to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages of the school-children ranged from 5 to 10 from 8 to 11 and from 7 to 19 years in the respective times.

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study, 1 year later one was 19 years old, but at the end of the study the ages ranged from 1 to 17.

The youngest mother was 20 years old and the oldest 45 years when they entered the study and the youngest father was 25 and the oldest 63 years of age.

Social grouping of the families. Most of the families belonged to the middle socio-economic class (5a). 3 families were of the upper class (5.8 per cent) and 13 from the

Table 2. Mean and median ages of the study groups

Study group	Age					
	April 1963		September 1, 1966		August 31, 1967	
	Mean	Median	Mean	Median	Mean	Median
Nursery group						
Infant	9½ mo	8 mo	11 mo	3 mo	7½ mo	8 mo
Family group						
Infants	9 mo	8 mo	1 yr 4½ mo	1 yr 3 mo	2 yrs 4 mo	2 yrs 3 mo
Children 0–2 yrs	3½ yrs	3 yrs	3 yr	4 yrs	5 yrs	3 yrs
School-children 3–10 yrs	8 yrs	8 yrs	9½ yrs	8 yrs	9½ yrs	9 yrs
Children 11–17 yrs	14 yrs	14 yrs	15 yrs	13½	14 yrs	14 yrs
Mothers	32 yrs	31 yrs	35 yrs	32 yrs	33 yrs	33 yrs
Fathers	34 yrs	34 yrs	36 yrs	34 yrs	35 yrs	35 yrs

Table 1 Mean number of participants in the study by month

	Nursery group		Family group			
	Infants	Infants	Children 0-6 yrs	School children 7-10 yrs	Children 11- yrs	Parents
1965 Sept.	16	33	29	33	10	60
Oct.	15	35	29	35	10	60
Nov.	10	34	28	33	10	60
Dec.	16	33	28	33	10	60
1966 Jan.	17	33	7	34	8	58
Feb.	16	33	7	34	7	58
Mar.	14	37	31	38	9	63
Apr.	15	34	45	54	16	92
May	15	34	44	54	16	90
June	14	41	31	4	13	80
July	15	36	26	34	10	72
Aug.	15	43	31	4	13	80
Sept.	14	49	40	30	14	86
Oct.	15	48	40	49	1	83
Nov.	15	4	39	49	1	80
Dec.	17	47	30	49	11	88
1967 Jan.	10	4	38	47	10	78
Feb.	14	43	3	43	10	76
Mar.	13	43	3	43	10	76
Apr.	13	43	37	43	10	76
May	14	43	37	44	10	77
June	14	33	7	33	7	83
July	14	7	19	40	8	60
Aug.	16	35	27	30	9	67
mean	15	40	33	40	10	73

Family population Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles:

— **Infants.** All children under 2 years of age at enrolment in September 1965 or April 1966. The total number of infants was 60: 33 girls and 27 boys. The mean number of infants in the study was 40.3, the weekly mean the same and the median number was 41 infants.

— **Children 2-6 years of age.** All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group. The total number of children in this group was 47: 20 girls and 27 boys. The mean number of children 2-6

years of age in the study was 30.0, the weekly mean the same and the median 32.

— **School-children 7-10 years of age.** All children in elementary schools during the study period up to 10 years old were included in this group. There were 60 children, 31 girls and 24 boys. The mean number of school children aged 7-10 years in the study was 40.6, the same as the weekly mean, the median was 41.

— **Children 11 years old and older.** All the children aged 11 years or more at enrolment were in this group. There were only 19 such children. The mean number of older children in the study was 10.5, the weekly mean the same and the median 10 children.

The mean number of parents in the study was 72.7, the mean weekly number 72.9 and the median 76.

The mean monthly numbers of persons under observation in each of these age groups are shown in Table 1.

There is a decline in the mean monthly number of participants during the summer months due to loss of children and families from observation during their vacations. Eleven families dropped out of the study 4 families because they moved out of town after participation for on an average one year three (two of them in the beginning of the study one after 9 months) because of the laborious study procedures. Three families did not want to cooperate because of the bleedings and were released after being in the study for 4, 9 and 11 months. One infant entered a day-nursery and the family was released after 16 months participation in the study. Two persons in the oldest child group were released: one was sent to a tuberculous sanatorium, the other left home to study elsewhere.

Description of the population

The mean and the median age of each study group was calculated at the beginning, middle and end of the study. The results are shown in Table 2. In the nursery group the standard deviations of the mean ages were

6½, 8½ and 7½ months, respectively. On these occasions the youngest infants were 2 months of age, and at the end of the study the oldest infant was 7 years 7 months old.

In the family infants the standard deviations of the mean ages were 5½, 7½ and 9½ months, respectively. In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged 7-6 years, the age range was from 7 to 6 years, from 7 to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages of the school-children ranged from 5 to 10 from 6 to 11 and from 7 to 12 years in the respective times.

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study 1 year later one was 19 years old, but at the end of the study the ages ranged from 12 to 17.

The youngest mother was 22 years old and the oldest 45 years when they entered the study and the youngest father was 20 and the oldest 63 years of age.

Social grouping of the families. Most of the families belonged to the middle socio-economic class (36). 3 families were of the upper class (6.8 per cent) and 13 from the

Table 2. Mean and median ages of the study groups

Study group	Age					
	September 1, 1963		September 1, 1964		August 31, 1967	
	Mean	Median	Mean	Median	Mean	Median
Nursery group						
infants	9½ mo	8 mo	11 mo	3 mo	7½ mo	3 mo
Family group						
infants	9 mo	8 mo	1 yr 4½ mo	1 yr mo	2 yrs 4 mo	2 yrs mo
children 2-6 yrs	3½ yrs	2 yrs	3 yrs	4 yrs	5 yrs	5 yrs
school-children 7-10 yrs	8 yrs	8 yrs	8½ yrs	8 yrs	9½ yrs	9 yrs
children 11-17 yrs	14 yrs	14 yrs	12 yrs	13 yrs	14 yrs	14 yrs
mothers	32 yrs	31 yrs	32 yrs	32 yrs	32 yrs	33 yrs
fathers	34 yrs	34 yr	34 yrs	34 yrs	35 yrs	35 yrs

Table 1 *Mean number of participants in the study by month*

	Nursery group		Family group			
	Infants	Infants	Children 3-6 yrs	School-children 7-10 yrs	Children 11- yrs	Parents
1963 Sept	15	30	29			
Oct.	15	33	29	33	10	62
Nov	16	34	29	33	10	62
Dec.	16	33	28	33	10	60
1966 Jan.					10	60
Feb.	17	33	27	34	8	59
Mar	16	33	27	34	7	58
Apr	14	37	31	38	9	63
May	13	54	45	54	16	93
June	13	32	44	54	16	90
July	14	41	31	42	13	80
Aug.	13	36	26	34	10	72
Sept	15	43	31	42	13	80
Oct	14	49	40	50	14	80
Nov	15	48	40	49	1	83
Dec.	15	4	39	49	13	82
	17	47	39	49	11	83
1967 Jan.						
Feb.	16	43	38	47	10	78
Mar	14	43	3	45	10	76
Apr	13	43	37	43	10	76
May	13	43	37	43	10	76
June	14	43	37	44	10	76
July	14	35	27	28	7	77
Aug	14	27	19	20	5	65
	16	23	27	30	9	60
mean	15	40	33	40	19	73

Family population: Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles

— *Infants.* All children under 2 years of age at enrolment in September 1963 or April 1966. The total number of infants was 60: 33 girls and 27 boys. The mean number of infants in the study was 40.3 the weekly mean the same and the median number was 41 infants.

— *Children 2-6 years of age.* All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group. The total number of children in this group was 47: 20 girls and 27 boys. The mean number of children 2-6

years of age in the study was 30.0 the weekly mean the same and the median 32

— *School-children 7-10 years of age.* All children in elementary schools during the study period up to 10 years old were included in this group. There were 65 children: 31 girls and 24 boys. The mean number of school children aged 7-10 years in the study was 40.6 the same as the weekly mean the median was 41

— *Children 11 years old and older.* All the children aged 11 years or more at enrolment were in this group. There were only 19 such children. The mean number of older children in the study was 10.5 the weekly mean the same and the median 10 children.

The mean number of parents in the study was 72.7 the mean weekly number 72.9 and the median 76

The mean monthly numbers of persons under observation in each of these age groups are shown in Table 1.

There is a decline in the mean monthly number of participants during the summer months due to loss of children and families from observation during their vacations. Eleven families dropped out of the study 4 families because they moved out of town after participation for on average one year three (two of them in the beginning of the study one after 9 months) because of the laborious study procedure. Three families did not want to cooperate because of the bleedings and were released after being in the study for 4, 9 and 11 months. One infant entered a day-nursery and the family was released after 16 months participation in the study. Two persons in the oldest child group were released: one was sent to a tuberculosis sanatorium, the other left home to study elsewhere.

Description of the population

Age. The mean and the median age of each study group was calculated at the beginning, middle and end of the study. The results are shown in Table 2. In the nursery group the standard deviations of the mean ages were

5½, 8½ and 7½ months, respectively. On these occasions the youngest infants were 2 months of age, and at the end of the study the oldest infant was 9 years 7 months old.

In the family infants the standard deviations of the mean ages were 5½, 7½ and 9½ months, respectively. In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged 1—6 years, the age range was from 2 to 6 years, from 2 to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages of the school-children ranged from 8 to 10, from 6 to 11 and from 7 to 11 years in the respective times.

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study. 1 year later one was 19 years old, but at the end of the study the ages ranged from 17 to 17.

The youngest mother was 21 years old and the oldest 45 years when they entered the study and the youngest father was 25 and the oldest 53 years of age.

Social grouping of the families. Most of the families belonged to the middle socio-economic class (55). 3 families were of the upper class (5.8 per cent) and 13 from the

Table 2. Mean and median ages of the study groups

Study group	Age					
	September 1 1963		September 1 1966		August 31, 1967	
	Mean	Median	Mean	Median	Mean	Median
Nursery group						
Infants	9½ mo	8 mo	11 mo	3 mo	1½ mo	3 mo
Family group						
Infants	9 mo	8 mo	1 yr 4½ mo	1 yr 3 mo	2 yrs 4 mo	2 yrs 5 mo
Children 1—4 yr	2½ yrs	3 yrs	3 yrs	4 yrs	3 yrs	3 yrs
School children 7—10 yrs	8 yrs	8 yrs	8½ yrs	8 yrs	9½ yrs	9 yrs
Children 11—17 yrs	14 yrs	14 yrs	17 yrs	13 yrs	14 yrs	14 yrs
Mothers	33 yrs	31 yrs	33 yrs	33 yrs	33 yrs	33 yrs
Fathers	34 yrs	34 yrs	34 yrs	34 yrs	35 yrs	35 yrs

lower class (29.2 per cent) Usually the homes were clean and good care was taken of the children. Twenty-eight families lived in modern flats, but some of these were rather small for the size of the family. Four families had houses of their own. Sixteen families lived in definitely overcrowded conditions. Some of these homes were in old frame-houses not supplied with modern conveniences. Four of these families moved to better quarters during the study period. In 7 families the care of the children was not adequate as was indicated by the fact that the children were not properly clothed, dental care was neglected and the diet was not well balanced.

Nine of the mothers were in full time employment outside the home and 8 were in occasional or part time employment.

Residence of the families The families in the study mainly resided in 4 areas within a distance of 2 miles from the hospital. In the beginning of the study one-third lived in the central city area, the others were living in 3 housing estates in the other end of the hospital which is situated on the border of the central city area. Four of the families moved to new housing areas far from the hospital but remained in the study.

After April 1966 when the new group of families was recruited, one-third still lived in the central city area. Almost one-third of the families now resided in each of the other two housing estates. During the last year of the study the people from the central city area moved to the third housing estate and some dropped out of the study. At the end the families were distributed evenly in the central city area and the 3 housing estates at the outer edge of the city.

Size of the families. Half of the 48 families included in the study consisted of 5 members, 16 families had 6 members, 4 had 7 members, 3 had 8 and one family had 9 members.

School attendance The mean number of children attending nursery play groups was 6 and kindergarten 9. The mean number of

children in elementary public schools was the highest number being 45 in fall 1966. Average 7 of the children in the family group were attending high schools.

Of the oldest children 3 were already working.

Medical status In the nursery group there were 2 premature infants, 4 with congenital malformations, 2 microcephalics, one mentally retarded with a cleft palate and one infant with paralysis of the lower extremities, who had been operated on for hydrocephalus. These last two infants stayed for the longer times in the nursery. Of the infants in the family group 4 had atopic dermatitis, one had congenital heart disease and one had congenital malformation of the urinary tract. One child aged 2 years had atopic dermatitis. Of the school-children one had asthma and one was a diabetic. One of the fathers had congenital heart disease.

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Duration of observation

Nursery group The total observation time of the infants in the nursery group was 342 person-months, resulting in a mean observation period of 60 months per infant. One infant was resident for the period of 2 years.

Family group The total observation time

42 infants was 1031 person-months, resulting in a mean observation of 17 months per infant. The children aged from 9 to 6 years were observed for a total of 864 person-months, 18 months per child. The total observation time for school-children was 1041 person-months, averaged 19 months per child. The oldest children were under observation for 264 person-months, 14 months per child. The total person-months of observation were 4977 for the family group, including the vacation periods.

STUDY PROCEDURE

The surveillance was carried out from September 1 1965 to August 31, 1967.

Methods of observation

At the start of the study all the children were examined by the author at child welfare centers. The examination was repeated in summer 1966 and 1967. Home visits were made by the author 3 times a year to all families from which no respiratory illnesses had been recently reported.

The aim was to study all acute respiratory illnesses which occurred among the participants. No daily health records were kept in the families. The mothers were asked to contact the author by telephone when respiratory symptoms occurred in any member of the family. The mothers kept records of symptoms until the patient was healthy. The parents were not observed so closely as the children, but were asked to report their respiratory illnesses, particularly when other members of the family had respiratory symptoms at the same time.

In the nursery the rectal temperature of each child was measured twice a day. Careful records were kept of all respiratory and other symptoms of illness. Acute respiratory illnesses were immediately reported to the author.

Collection of specimens

When a new case of respiratory illness was reported, the members of the family group were seen at the outpatient clinic of the Children's Hospital or sometimes, when older children were ill, the specimens were collected at home. All the specimens from the infants of the nursery group were taken in the nursery.

Pharyngeal swabs for virus isolation were taken from each patient with respiratory symptoms. The pharynx was firmly swabbed with 4 cotton applicators as described by Berglund *et al.* (10). From the infants of the nursery group rectal swabs were also collected from April 1966 onwards.

Acute and convalescent phase blood samples were collected during each respiratory illness. All blood samples were obtained by venipuncture, in the older infants, children and adults from cubital veins, in the youngest infants from scalp veins. The blood (5 ml) was allowed to drip from the needle to the centrifuge tube. The convalescent phase blood sample was taken 10–14 days after the acute phase sample except in infants, where the period was 14–21 days. Supplementary blood samples were sometimes taken in the nursery group 4–6 weeks after the onset of the illness. If the infant was very young, and delay of the antibody response was suspected (7). During an epidemic of RS virus in the nursery described elsewhere (29) when the middle ear aspirates from infants with otitis media were cultured for isolation of viruses and bacteria, the infants were bled simultaneously with the ear-drum punctures. The convalescent phase blood samples were taken on home visits more often than the acute phase samples.

In cases in which a second acute respiratory infection followed immediately after the first, a single blood sample served as the convalescent phase sample for the first and as the acute phase sample for the second illness.

lower class (29.2 per cent). Usually the homes were clean and good care was taken of the children. Twenty-eight families lived in modern flats, but some of these were rather small for the size of the family. Four families had houses of their own. Sixteen families lived in definitely overcrowded conditions. Some of these homes were in old frame-houses not supplied with modern conveniences. Four of these families moved to better quarters during the study period. In 7 families the care of the children was not adequate, as was indicated by the fact that the children were not properly clothed, dental care was neglected and the diet was not well balanced.

Nine of the mothers were in full time employment outside the home and 8 were in occasional or part time employment.

Residence of the families The families in the study mainly resided in 4 areas within a distance of 2 miles from the hospital. In the beginning of the study one-third lived in the central city area, the others were living in 3 housing estates in the other side of the hospital which is situated on the border of the central city area. Four of the families moved to new housing areas far from the hospital but remained in the study.

After April 1966 when the new group of families was recruited, one-third still lived in the central city area. Almost one-third of the families now resided in each of the other two housing estates. During the last year of the study the people from the central city area moved to the third housing estate and some dropped out of the study. At the end the families were distributed evenly in the central city area and the 3 housing estates at the outer edge of the city.

Size of the families Half of the 48 families included in the study consisted of 5 members, 16 families had 6 members, 4 had 7 members, 3 had 8 and one family had 9 members.

School attendance The mean number of children attending nursery play groups was 6 and kindergarten 9. The mean number of

children in elementary public schools was 3, the highest number being 45 in fall 1966. On average 7 of the children in the family group were attending high schools.

Of the oldest children 3 were already at work.

Medical status In the nursery group there were 2 premature infants, 4 with congenital malformations, 2 microcephalics, one mentally retarded with a cleft palate and one infant with paralysis of the lower extremities, who had been operated on for hydrocephalus. These last two infants stayed for the longest times in the nursery. Of the infants in the family group 4 had atopic dermatitis, one had congenital heart disease and one had a congenital malformation of the urinary tract. One child aged 2 years had atopic dermatitis. Of the school-children one had asthma and one was a diabetic. One of the fathers had congenital heart disease.

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nts or re-examinations at the outpatient were performed. The mothers were instructed to measure the temperatures of the patients until they had returned to normal. The patient was considered to be cured when all signs of respiratory illness had disappeared.

On the convalescent phase visit the history of the current illness was obtained, the patient examined to ensure that no signs of respiratory illness remained and the final clinical diagnosis was made. The diagnostic criteria used and down by Tyrrell (69) and commonly accepted in pediatric practice were used to classify the acute respiratory illnesses.

The length of the respiratory illness was mostly based on the persistence of nasal discharge, particularly in infants. Fairly often during such periods, exacerbation in the respiratory symptoms occurred. In such cases it was taken as a new illness and marked termination of the preceding illness, although no return to complete health had occurred.

Data processing

The basic information on each participant was coded on an IBM card. For each respiratory illness another IBM card was prepared, containing personal identification data, dates of onset of illness, recovery and sampling, results of virus isolation, coded clinical diagnosis, information on temperature, signs and symptoms and the CF results. The results of HI and neutralization test with 4-fold or greater rise in antibody titer were recorded on a separate card. For information on other than respiratory illnesses observed during the study an additional card was prepared, containing the date and coded clinical diagnosis of the illness.

The data were processed at the Institute of Applied Mathematics, University of Turku, with an IBM 1130 Computer rented from IBM. The computer was programmed to search

for significant serologic rises (4-fold or greater rise of antibody titer in CF HI or neutralization tests) and to combine these with relevant virus isolations. Each respiratory illness was thus labeled with the specific virus etiology.

The weekly and total numbers of new cases of respiratory illnesses adequately studied were counted from the dates of obtaining the pharyngeal swabs. The duration of the respiratory illness was calculated by the computer from the dates of onset and recovery. The computer selected the data of the acute respiratory infections to obtain the other information presented.

The computer was also programmed to calculate the ages of the study population and the weekly mean numbers of participants from the data on the basic personal information cards. The mean weekly percentages of individuals with respiratory symptoms were calculated by the computer from the dates of onset and recovery and the mean weekly numbers of participants.

Statistical methods

The degree of statistical significance has been determined by Student's t-test and chi-square test. The IBM computer performed the chi-square tests. The difference between proportions is said to be almost significant, if $0.01 < p \leq 0.05$ significant if $0.001 < p \leq 0.01$ and highly significant, if $p \leq 0.001$.

LABORATORY METHODS

Cell cultures

The cell cultures used for virus isolation were HeLa, U (continuous human amnion cell line) and primary monkey kidney cells. Their origin and the techniques used with these cells have been described in detail by Mänty

Table 3 *Specimens collected*

Study group	Number of specimens				
	Virus isolation		Serum		
	Pharyngeal swabs	Rectal swabs	Acute phase	Convalescent	Supplementary
Nursery group					
Infants	180	153	10	181	31
Family group					
Infants	509	1	190	303	—
children 2-6 yrs	106	3	164	110	—
school-children 7-10 yrs	35	—	56	57	—
children 11- yrs	7	—	7	7	—
parents	24	—	33	33	—
Total	600	158	350	593	31

Rectal swab specimens were also taken from a few patients of the family group with respiratory illness accompanied with diarrhea. Table 3 shows the total numbers of specimens. A convalescent phase blood sample was sometimes not available. Some specimens were contaminated and in addition, a few were lost during laboratory processing.

All the serum specimens were tested by the complement fixation (CF) technique using the following antigens: RS virus, parainfluenza viruses types 1, 2 and 3, influenza viruses types A and B, mumps virus, adenovirus group herpes simplex and *M. pneumoniae*. The other serologic tests performed were based on isolations of viruses and epidemiologic findings. Nearly all sera were tested in the hemagglutination inhibition (HI) test for antibodies to adenovirus types 1, 2 and 5. With adenovirus types 6, 3 and 7, HI tests were performed on fewer specimens, mostly only when these viruses had been isolated. Paired sera with a rise or high titer of parainfluenza virus antibodies in the CF test were examined in the HI test for antibodies to parainfluenza types 1, 2 and 3. Similarly, sera with an influenza A antibody rise in the CF test were tested in HI to influenza A2 antibody.

The sera from patients with RS virus isolations but no rise in the CF test to RS antibody were tested by neutralization with B virus. Likewise, the paired sera showing 2 fold rise in RS antibody in the CF test were tested by neutralization. Neutralization test with Coxsackie B5 and ECHO 9 viruses were restricted to individuals with these isolations and their immediate contacts. The sera from patients with Coxsackie B type 2 isolation and their contacts were tested in the CF test against Coxsackie B type 1-5.

Clinical examination

On the visit at the acute phase of the disease a careful medical history was taken and a clinical examination performed. Upon initial examination the respiratory illnesses were clinically diagnosed and if necessary chest roentgenograms and laboratory tests were taken. The children with otitis media were sent to otologist. The necessary medication was prescribed. Some seriously ill children were remitted to hospital.

The course of the illnesses was followed. The staff in the nursery and the mothers kept in contact by telephone and often home

visits or re-examinations at the outpatient clinic were performed. The mothers were instructed to measure the temperatures of the patients until they had returned to normal. The patient was considered to be cured when all signs of respiratory illness had disappeared.

On the convalescent phase visit the history of the current illness was obtained, the patient examined to ensure that no signs of respiratory illness remained and the final clinical diagnosis was made. The diagnostic criteria laid down by Tyrrell (89) and commonly accepted in pediatric practice were used to classify the acute respiratory illnesses.

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LABORATORY METHODS

Cell cultures

The cell cultures used for virus isolation were HeLa, U (continuous human amnion cell line) and primary monkey kidney cells. Their origin and the techniques used and how cells have been maintained in culture are

juuri (44) GMK and LLC-MK₂ cell cultures were used in enterovirus neutralization tests and in CF antigen preparations.

The growth medium for HeLa cells consisted of 55 per cent Hanks balanced salt solution, 30 per cent inactivated human serum and 15 per cent tryptose phosphate broth (TPB) (Difco, distributed by Microbiological Laboratory Laaketeidas Orion Oy Helsinki, Finland). The growth medium for U cells consisted of 75 per cent lactalbumin hydrolysate (LAH) (Nutritional Biochemical Corporation Cleveland, Ohio) in Hanks solution in a final concentration of 5 mg LAH/l and 25 per cent inactivated calf serum. The inoculum was 100 000 HeLa and U cells per tube. The maintenance medium (44) of HeLa and U cells consisted of Eagle's minimum essential medium (MEM) supplemented with 5 per cent inactivated horse serum and 5 per cent TPB. However for rectal swab specimens the maintenance medium of U cells consisted of Parker's medium 199 (Parker) supplemented with 0.1 per cent bovine serum albumin (Bovine serum albumin fraction V Armour Pharmaceutical Co distributed by Microbiological Laboratory Laaketeidas Orion Oy Helsinki Finland). From June 1966 this medium was changed to MEM supplemented with 2 per cent inactivated chicken serum.

Primary monkey kidney cells were obtained from the State Bacteriological Laboratory Stockholm, Sweden. They were grown in a medium consisting of 70 per cent LAH solution, 20 per cent inactivated calf serum and 10 per cent TPB. The maintenance medium was Parker with 0.1 per cent bovine serum albumin.

GMK cells (a continuous line of African green monkey kidney cells) were obtained from Dr Arne Svedmyr Central Bacteriological Laboratory Stockholm City Stockholm, Sweden. The growth medium consisted of 89 per cent MEM 10 per cent inactivated calf serum and 1 per cent L-arginine solution (1.74 gm/l). The GMK cultures were treated

as HeLa and U cell cultures (44). During a growth period of two weeks the media was replaced once and a one-liter Roux bottle yielded 80 tissue culture tubes. GMK cells were maintained in 97 per cent MEM with per cent inactivated calf serum, 1 per cent L-arginine solution (1.74 gm/l) and additional 0.1 per cent dextrose.

LLC-MK₂ cells (a continuous line of monkey kidney cells) were obtained from the National Institutes of Health, Bethesda, Md. The growth medium consisted of basal medium (Eagle) Diploid (BME) (Grand Island Biological Company Grand Island, New York) with 10 per cent inactivated calf serum. Cells grown in a Roux bottle were treated with 10 ml of 0.25 per cent trypsin in Hanks solution, the trypan was decanted and the bottle was incubated at 37°C for 10–15 min. Then the cells were suspended in the growth medium and 80 tissue culture tubes were inoculated from one Roux bottle. The maintenance medium consisted of BME Diploid supplemented with 1 per cent inactivated fetal calf serum (Microbiological Laboratory Laaketeidas Orion Oy Helsinki, Finland).

The maintenance media contained 40 units/ml penicillin, 400 µg/ml streptomycin, 25 units/ml nystatin and 5 µg/ml amphotericin B. All tissue culture media contained 0.002 per cent phenol red. The pH was adjusted with 7 per cent NaHCO₃.

Virus isolation

The pharyngeal and rectal swab specimens were inoculated directly into tissue culture tubes by the technique described in detail by Berglund *et al* (10). Duplicate cultures in HeLa U and primary monkey kidney cells were inoculated by one cotton applicator per cell line. The tissue culture tubes used for direct inoculation contained 1 ml of maintenance medium instead of the regular 1 ml to prevent drying of cells during transport.

ne of the applicators was placed in a tube containing ml Hanks's solution with 0.1 % bovine albumin, 500 units penicillin/ml, 500 U streptomycin/ml, 25 units mycostatin/ml and 5 µg amphotericin B/ml. This tube was stored at -60°C .

The cultures of the pharyngeal swab specimens were incubated in stationary racks at 35°C and those of the rectal swab specimens at 37°C . In the beginning of the study the maintenance medium was changed every 5th day but after spring 1966, it was changed twice a week. The HeLa cell cultures were maintained 12–14 days and when spontaneous degeneration of cells occurred a blind passage was made. In U and monkey kidney cells the cultures were usually maintained for 14 days. The cultures were examined for cytopathogenic effect (CPE) every second day. When CPE was suspected, a second passage was made. The monkey kidney cell cultures were tested for hemadsorption with human type O erythrocytes at 4°C on the 5th and 10th days.

The isolated viruses were identified according to the following procedures.

The isolates showing syncytial CPE were tested in complement fixation (CF) reaction using paired sera from patients with at least 16-fold antibody rise to respiratory syncytial (RS) virus (10).

The isolates positive in hemadsorption and with hemagglutinating activity were identified by the hemagglutination inhibition (HI) test, using anti parainfluenza virus guinea pig sera and anti-influenza A2 rabbit sera. Some of the hemadsorbing isolates failed to agglutinate sufficiently. These were identified by neutralization with the parainfluenza virus human sera or by the CF reaction, using paired patient sera with an antibody rise to influenza A virus.

The adenovirus isolates were identified by the presence of adenovirus group-specific antigen in the CF test (44). The adenovirus types were identified by the HI test with type-

specific immune rabbit sera. Herpes simplex viruses were identified by the neutralization test, using an immune rabbit serum (45).

The isolates which could not be typed by the above-described methods were subjected to neutralization tests with enterovirus antisera acquired from the Wellcome Research Laboratories, Beckenham, England (Coxsackie B type 5 ECHO 6 9) and from the National Institutes of Health, Bethesda, Md. (Coxsackie B type 1–4). The typing results of one parainfluenza type 1 strain, and two Coxsackie B type 5 strains and three ECHO 9 strains were kindly confirmed at the Respirovirus Unit and Enterovirus Infection Unit at the National Communicable Disease Center, Atlanta, Georgia.

Serologic methods

Complement fixation test

Procedure. The microtechnique of Sever (61) was used. Veronal — buffered diluent (VBD) with 0.1 per cent gelatine was used as diluent (30). Complement was fresh pooled guinea pig serum stored in small volumes at -60°C .

The hemolytic system consisted of equal parts of 2 per cent sheep erythrocytes and a dilution of hemolysin containing two full units. The tests were performed with 3–4 units of antigen. After addition of the hemolytic system, the plates were incubated at 37°C for 1 hour and shaken by hand every 15 min. Then the plates were placed at 4°C for 1–2 hours and read by visual estimation of the degree of hemolysis. The inhibition of hemolysis was recorded from 4+ to — and readings of 4+ and 3+ were considered positive.

A control complement titration in the presence of each antigen, the serum controls and the titration of a known positive serum for each antigen were included in each series of CF tests. All the sera of one patient were examined in the same series of CF tests.

Intigens All tissue culture antigens were prepared in Roux bottles and harvested when the cells showed complete CPE usually on the 4th to 7th day after inoculation. The cells were detached and disrupted by freezing and thawing.

Adenovirus antigen was prepared from adenovirus type 5 in HeLa cells (44). The HeLa maintenance medium containing horse serum was used. RS virus antigen was prepared with the Randall strain in U cells with the maintenance medium supplemented with horse serum (10). Parainfluenza virus antigens types 2 and 3 (strains obtained from WHO International Reference Centre for Respiratory Virus Diseases, Harvard Hospital Salisbury, Wiltshire) were prepared in U cells. The maintenance medium contained MEM supplemented with 5 per cent horse serum.

Parainfluenza virus type 1 mumps and influenza antigens were obtained from the State Serum Institute Helsinki Finland. Parainfluenza virus type 1 antigen was a Sendai antigen in allantoic fluid from embryonated eggs. The mumps antigen was also in allantoic fluid and was prepared with the Enders strain. Influenza A2 antigen was prepared with strain influenza A2/Singapore/57 and influenza B antigen with influenza B/Lee strain both in allantoic fluids.

Mycoplasma pneumoniae (Eaton PPL0) antigen was kindly supplied by Dr. Eli Jansson Municipal Bacteriological Laboratory Turku Hospital Helsinki Finland (36).

Herpes simplex antigen was prepared in HeLa cells or in human fibroblast cultures. The maintenance medium for HeLa cells was supplemented with horse serum. Human fibroblasts were grown in MEM supplemented with 10 per cent inactivated calf serum; the maintenance medium was the same with 3 per cent inactivated calf serum.

Antigens to Coxsackie B types 1-5 were prepared in U cells. The maintenance medium was MEM supplemented with 5 per cent horse serum.

Hemagglutination inhibition test

Procedure The hemagglutination and hemagglutination inhibition tests were performed by the microtitration method of Ser (61) with the following modifications. Phosphate buffered saline was used as diluent. Disposable microtiter U plates (Linbro Chemical Co. Inc., New Haven Conn.) were used in all HI tests. The volume of the antigen and serum dilutions was 0.025 ml, and the volume of erythrocyte suspensions 0.05 ml.

In HI tests, 4 antigen units were used. The test was incubated 1 hour at room temperature before the erythrocytes were added. All sera from one patient were included in the same HI test.

Identities. Rat and monkey erythrocytes were used. The rat erythrocytes were obtained by heart puncture from rats of Long Evans strain. The African green monkey erythrocytes were obtained from State Bacteriological Laboratory Stockholm Sweden. The erythrocytes were washed three times with phosphate buffered saline and stored as a 10 per cent suspension in Alsevers solution (13). The erythrocytes were used as a 0.5 per cent suspension. The rat erythrocytes were suspended in 1:100 dilution of normal rabbit serum (56).

The adenovirus HA antigens of types 1-7 were produced by the same method as the adenovirus (F) antigen. For the antigens of types 1, 2 and 5 a 1:100 dilution of type 6 immune serum was used as diluent to make agglutination complete (58). Similarly for type 6 antigen a dilution of type 2 immune serum was used.

The sera were adsorbed with kaolin and rat and monkey erythrocytes by the method described by Halonen *et al.* (31) and heat inactivated at 56°C for 30 min. After the erythrocytes were added, the plates were incubated at 37°C for 1 hour.

Parainfluenza viruses. Human type O erythrocytes were used. They were treated

Described above with rat erythrocytes and used as a 0.4 per cent suspension.

The parainfluenza virus type 1 antigen was the same Sendai antigen as in the CF test. The type 2 and 3 antigens were prepared in U cells. The maintenance medium was Parker supplemented with 0.4 per cent bovine serum albumin.

The sera were treated with 11/100 potassium periodate (22) and heat-inactivated at 56°C for 30 min. When the erythrocyte suspension was added, the plates were incubated at room temperature.

Influenza A2 virus. Chicken erythrocytes were treated in the same way as rat erythrocytes and used as a 0.5 per cent suspension.

The influenza A₁ antigen was in allantoic fluid harvested from embryonated eggs after inoculation with influenza A2/Finland/1/65 strain obtained from the State Serum Institute Helsinki, Finland.

The treatment of sera and the test procedure were the same as for parainfluenza virus III test.

Neutralization test

Procedure - All viruses were diluted to contain approximately 100 TC₅₀ units of virus per 0.1 ml. The sera were inactivated at 56°C for

30 min. The patient sera were diluted 2 fold from the initial dilution of 1:4. The virus and serum dilutions in equal volumes were mixed, incubated as described later and inoculated in 0.2 ml volumes into duplicate tissue culture tubes. A control titration of the virus was always included in the test. The test was read when control tubes showed a CPE of 3+ to 4+. The titer was the highest serum dilution with a CPE of 1+ or less. All the sera from one patient were included in the same neutralization test.

RS virus The RS virus strain used in the neutralization tests was a patient strain from this study. It had been identified by the CF method (9). The test was performed in U cells. The incubation time for virus-serum mixture was 1 hour at room temperature. The tissue culture medium was changed on the day following inoculation.

Coxsackie B type 5 virus. The serum-virus mixture was incubated 2 hours at 37°C (48). The isolates were typed by neutralization in GMK cells. The neutralization tests of patient sera were performed in LLC-MK cells.

ECHO 9 virus. The maintenance medium was BME Diploid with 1 per cent fetal calf serum. The isolates were typed in GMK cells, the serum neutralizations performed in LLC-MK₂ cells. The procedure was the same as in the Coxsackie B type 5 neutralization.

Antigens All tissue culture antigens were prepared in Roux bottles and harvested when the cells showed complete CPE usually on the 4th to 7th day after inoculation. The cells were detached and disrupted by freezing and thawing.

Adenovirus antigen was prepared from adenovirus type 5 in HeLa cells (44). The HeLa maintenance medium containing horse serum was used. RS virus antigen was prepared with the Randall strain in U cells with the maintenance medium supplemented with horse serum (10). Parainfluenza virus antigens types 2 and 3 (strains obtained from WHO International Reference Centre for Respiratory Virus Diseases, Harvard Hospital Salisbury Wiltshire) were prepared in U cells. The maintenance medium contained MEM supplemented with 5 per cent horse serum.

Parainfluenza virus type 1 mumps and influenza antigens were obtained from the State Serum Institute Helsinki Finland. Parainfluenza virus type 1 antigen was a Sendai antigen in allantoic fluid from embryonated eggs. The mumps antigen was also in allantoic fluid and was prepared with the Enders strain. Influenza A2 antigen was prepared with strain influenza A2/Singapore/57 and influenza B antigen with influenza B/Lee strain both in allantoic fluids.

Mycoplasma pneumoniae (Eaton PPLO) antigen was kindly supplied by Dr Eili Jansson Municipal Bacteriological Laboratory Aurora Hospital Helsinki Finland (36).

Herpes simplex antigen was prepared in HeLa cells or in human fibroblast cultures. The maintenance medium for HeLa cells was supplemented with horse serum. Human fibroblasts were grown in MEM supplemented with 10 per cent inactivated calf serum; the maintenance medium was the same with 3 per cent inactivated calf serum.

Antigens to Coxsackie B types 1-5 were prepared in U cells. The maintenance medium was MEM supplemented with 5 per cent horse serum.

Hemagglutination inhibition test

Procedure The hemagglutination and hemagglutination inhibition tests were performed by the microtitration method of Sevel (61) with the following modifications. I phosphate-buffered saline was used as diluent. Disposable microtiter U plates (Fibro Chemical Co. Inc. New Haven Conn.) were used in all HI tests. The volume of the antigen and serum dilutions was 0.025 ml and the volume of erythrocyte suspensions 0.05 ml.

In HI tests, 4 antigen units were used. The test was incubated 1 hour at room temperature before the erythrocytes were added. All sera from one patient were included in the same HI test.

Idenotivuses Rat and monkey erythrocytes were used. The rat erythrocytes were obtained by heart puncture from rats of Long Evans strain. The African green monkey erythrocytes were obtained from State Bacteriological Laboratory Stockholm Sweden. The erythrocytes were washed three times with phosphate-buffered saline and stored as a 10 per cent suspension in Alsevers solution (13). The erythrocytes were used as a 0.5 per cent suspension. The rat erythrocytes were suspended in 1:100 dilution of normal rabbit serum (56).

The adenovirus HA antigens of types 1-7 were produced by the same method as the adenovirus CF antigen. For the antigens of types 1, 2 and 5 a 1:100 dilution of type 6 immune serum was used as diluent to make agglutination complete (56). Similarly for type 6 antigen a dilution of type 2 immune serum was used.

The sera were adsorbed with kaolin and rat and monkey erythrocytes by the method described by Halonen *et al.* (31) and heat inactivated at 56°C for 30 min. After the erythrocytes were added the plates were incubated at 37°C for 1 hour.

Parainfluenza viruses Human type O erythrocytes were used. They were treated as

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1.

The respiratory illness rates per person year in the study groups were:

Nursery group:	
infants	6.3
Family group	
infants	2.5
children 3-6 years	1.5
school-children 7-10 years	0.7
children 11- years	0.3
parents	0.2

No significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illnesses. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by infants. Six infants had no symptoms of respiratory illness during their stay in the nursery.

In the family group, the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by infants. On the other hand, no acute respiratory illness was reported from 11 infants; 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged 3-6 years 6 had not experienced any episodes of acute respiratory illness. Among the school-children 3, and 1 among the oldest children 11 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory illness. Although the total rates of acute

respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer.

The curve of the cumulative respiratory illness rate in children aged 3-6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a similar pattern of acute respiratory illnesses was seen. The number of acute respiratory illnesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows:

Nursery group	
infants	33.3 per cent
Family group	
infants	9.6 per cent
children 3-6 years	5.3 per cent
school-children 7-10 years	1.7 per cent
children 11- years	1.0 per cent
parents	0.6 per cent

Every day on average 11 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average 4 of the children aged 3-6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses In total, information on 641 acute respiratory illnesses was reported. Of these illnesses, 197 occurred in the nursery and 444 among the family group. In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied. In the family group there was not always an opportunity to take the samples. In the

infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied, in children 2—6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated.

The total number of adequately studied respiratory illnesses was 598 of these 410 occurred in the family group. The number of adequately sampled acute respiratory illnesses in each group was:

Nursery group infants	188
Family group infants	308
children 2—6 years	106
school-children 7—10 years	55
children 11— years	7
parents	34

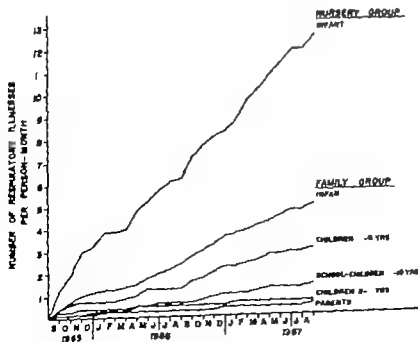


Fig 1 Cumulative incidence of acute respiratory illness by month. Each point on the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the time and the month denoted on the horizontal axis.

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1.

The respiratory illness rates per person-year in the study groups were

Nursery group	
infants	6.3
Family group	
infants	2.5
children 2-6 years	1.5
school-children 7-10 years	0.7
children 11- years	0.3
parents	0.3

No significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illnesses The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by 2 infants. Six infants had no symptoms of respiratory illness during their stay in the nursery.

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by 2 infants. On the other hand, no acute respiratory illness was reported from 11 infants. 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged 2-6 years 6 had not experienced any episodes of acute respiratory illness. Among the school children 25, and among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory illnesses. Although the total rates of acute

respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer.

The curve of the cumulative respiratory illness rate in children aged 2-6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a similar pattern of acute respiratory illnesses was seen. The number of acute respiratory illnesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows:

Nursery group	
infants	33.2 per cent
Family group	
infants	9.6 per cent
children 2-6 years	5.3 per cent
school-children 7-10 years	1.7 per cent
children 11- years	1.0 per cent
parents	0.6 per cent

Every day on average 6 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average 2 of the children aged 2-6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses In total, information on 641 acute respiratory illnesses was reported. Of these illnesses, 197 occurred in the nursery and 444 among the family group. In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied. In the family group there was not always an opportunity to take the samples. In the

infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied in children 2-6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated.

The total number of adequately studied respiratory illnesses was 598 of these 410 occurred in the family group. The number of adequately sampled acute respiratory illnesses in each group was

Nursery group infants	188
Family group infants	908
children 2-6 years	106
school-children 7-10 years	55
children 11- years	7
parents	34

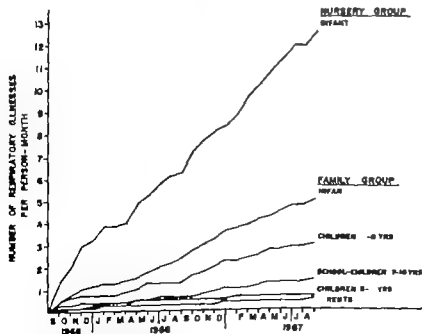


Fig 1. Cumulative rate of acute respiratory illnesses by month. Each point on the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the study and the month denoted on the abscissa.

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1.

The respiratory illness rates per person-year in the study groups were:

Nursery group	
infants	6.3
Family group	
infants	5
children 2-6 years	1.5
school-children 7-10 years	0.7
children 11- years	0.3
parents	0

No significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illnesses. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by 2 infants. Six infants had no symptoms of respiratory illness during their stay in the nursery.

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by 1 infant. On the other hand, no acute respiratory illness was reported from 11 infants. 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged 2-6 years 6 had not experienced any episodes of acute respiratory illness. Among the school children 15, and among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory illness. Although the total rates of acute

respiratory illnesses in the nursery and family infants were not the same a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer.

The curve of the cumulative respiratory illness rate in children aged 2-6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a similar pattern of acute respiratory illnesses was seen. The number of acute respiratory illnesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows:

Nursery group	
infants	33.3 per cent
Family group	
infants	9.6 per cent
children 2-6 years	5.3 per cent
school-children 7-10 years	1.7 per cent
children 11- years	1.0 per cent
parents	0.6 per cent

Every day on average 5 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average of the children aged 2-6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses. In total information on 641 acute respiratory illnesses was reported. Of these illnesses, 197 occurred in the nursery and 444 among the family group. In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied. In the family group there was not always an opportunity to take the samples. In the

infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied, in children 2-6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated.

The total number of adequately studied respiratory illnesses was 598, of these 410 occurred in the family group. The number of adequately sampled acute respiratory illnesses in each group was

Nursery group infants	188
Family group infants	208
children 2-6 years	106
school-children 7-10 years	55
children 11- years	7
parents	34

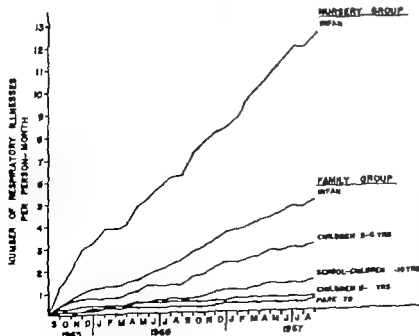


Fig 1 Cumulative rate of acute respiratory illnesses by month. Each point on the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the study and the month denoted on the abscissa.

Rate of the acute respiratory illnesses.

Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1.

The respiratory illness rates per person year in the study groups were

Nursery group	
infants	6.3
Family group	
infants	2.5
children 2-6 years	1.5
school-children 7-10 years	0.7
children 11-14 years	0.3
parents	0.

No significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illness. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by 9 infants. Six infants had no symptoms of respiratory illness during their stay in the nursery.

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by 9 infants. On the other hand, no acute respiratory illness was reported from 11 infants. 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged 2-6 years 6 had not experienced any episodes of acute respiratory illness. Among the school-children 13 and among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 23 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory illnesses. Although the total rates of acute

respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer.

The curve of the cumulative respiratory illness rate in children aged 2-6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a similar pattern of acute respiratory illnesses was seen. The number of acute respiratory illnesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows.

Nursery group	
infants	33.3 per cent
Family group	
infants	9.6 per cent
children 2-6 years	5.3 per cent
school-children 7-10 years	1.7 per cent
children 11-14 years	1.0 per cent
parents	0.6 per cent

Every day on average 5 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average of the children aged 2-6 years and one of the school-children had respiratory symptoms.

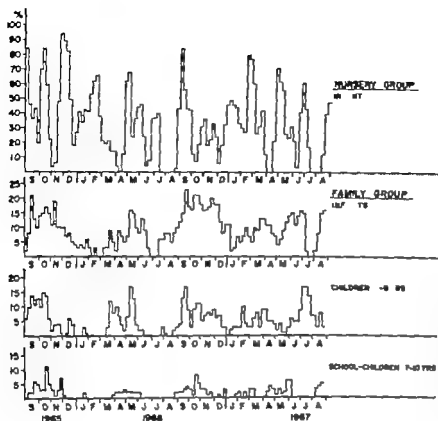


Fig. 2. Weekly prevalence of respiratory symptoms. The mean number of persons ill with respiratory symptoms expressed as a percentage of the mean number of individuals observed in the week & question.

Seasonal prevalence of respiratory symptoms Fig 2 shows the weekly prevalence of respiratory symptoms during the study period in the 4 study groups of infants and children. In the nursery group respiratory symptoms occurred in rather clearly distinguishable peaks, indicating new outbreaks of respiratory illness. In the infants of the family group the bar diagram is flattened and shows the seasonal variations rather than weekly outbreaks.

The high prevalence observed in July 1967 in the children aged 2—6 years was due to acute respiratory infections in two families only. The few illnesses reported in the school children aged 7—10 years coincided with the highest peaks of prevalence among the family infants. In the oldest children the highest prevalence of respiratory symptoms was 12 per cent in April 1966. Otherwise only one of these children had respiratory symptoms at any time. The highest prevalence observed in parents was 4 per cent in November 1965 and April 1967. The respiratory illnesses of the

parents were sporadic but in only 3 months were no symptoms of respiratory illness reported among the parents.

VIRUS ISOLATIONS AND SEROLOGIC TESTS

An acute respiratory illness was considered to have a diagnosed virus etiology according to the following principles.

Only virus isolations followed by a 4-fold or greater antibody rise relevant to the isolation were considered acceptable as evidence of the etiology. Some exceptions to this will be indicated in the sections concerned.

A 4-fold or greater rise in antibody titer in CF, HI and/or neutralization tests during a period not longer than 6 weeks was also considered acceptable as evidence of the etiology.

In Table 4 the etiology of the acute respiratory illnesses in both study groups is summarized.

Table 4. *Virus etiology in the 398 acute respiratory illnesses*

Virus group	Nursery group				Family group							
	Infants (184 illnesses)		Infants (206 illnesses)		Children 3-6 yrs (106 illnesses)		School-children 7-10 yrs (55 illnesses)		Children 11-15 yrs (7 illnesses)		Parents (24 illnesses)	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
RS	14	7.4	23	12.0	13	14.2	6	10.9	—	—	—	—
Parainfluenza	7	3.7	23	11.1	7	6.6	8	14.5	—	—	1	2.9
Influenza A2	—	—	4	1.9	3	4.7	4	7.3	—	—	2	5.9
Adeno	25	18.0	26	12.5	18	17.0	5	9.1	—	—	3	8.8
Coxsackie B	2	1.1	3	1.4	4	3.8	—	—	1	14.3	—	—
ECHO 9	—	—	2	1.0	1	0.9	—	—	—	—	1	2.9
Herpes simplex	—	—	1	0.5	—	—	—	—	—	—	—	—
Total positive rate	59/188	30.8	84/208	40.4	30/106	27.8	20/55	36.4	1/7	14.3	7/24	29.2

The total rate of detected virus infections in the acute respiratory illnesses of the infants in the family group was higher than in the infants of the nursery group ($p < 0.05$ t test). A greater variety of viruses were found in the infants of the family group. No signif-

icant difference in the rate of detected virus infections was observed between the three social groups of families.

The distribution of the acute respiratory illnesses with detected virus etiology was different among the infants in the nursery

Table 5. *Virus etiology of the 188 acute respiratory illnesses in the infants of the nursery group*

Virus	Virus isolation		Significant antibody rise	Total number of infections
	Pharyngeal swab	Rectal swab		
RS	14	—	12	14
Parainfluenza type 2	1	—	6	7
Adeno				
type 1	3	1	6	6
type 2	1(+2)	1(+2)	3(+2)	3(+2)
type 3	9(+2)	3(+1)	11(+1)	11(+1)
type 6	1	—	2	2
type 7	—	—	2	2
untyped	—	1	7 (+1)	7(+1)
Coxsackie B type 3	2	—	2	2
Total	33(+4)	5(+3)	53(+4)	58(+4)

Figures in parentheses indicate concurrent infection with RS virus, which was considered to be the main etiologic agent.

** Antibody rise in CF test.

and family groups ($p = 0.001$ chi-square test). The differences between the infants and the children aged 2-6 years in the family group were not statistically significant.

Infants of the nursery group The results of relevant virus isolations and antibody rises in the 188 acute respiratory illnesses in the infants of the nursery group are given in Table 5.

Of the original 57 pharyngeal and 10 rectal isolates, only 33 from pharyngeal and 2 from rectal swabs were considered to be etiologic agents (18.6 per cent positive). Fourteen adenovirus strains were detected in both pharyngeal and rectal swabs on the same

occasion and treated as a single isolation. In cases of virus isolation there was positive evidence that the Coxsackie B₁, and adenoviruses isolated were not etiologic agents in the current illnesses because virus had been isolated earlier or a significant serologic rise to the type had occurred earlier. Adenovirus types 1, 2 and 5 not followed by an antibody rise were isolated from infants in 3 cases RS or parainfluenza infections were simultaneously detected. One third of these adenovirus isolations sporadic.

The virus isolations and serologic response of the RS virus outbreak have been described

Table 5. Virus etiology of the 208 acute respiratory illnesses in the infants of the family group.

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	13	24	—3
Parainfluenza:			
type 1	4	0	0
type 2	1	3	3
type 3	4	8	9
untyped	3	5	5
Influenza A2	3	4	4
Adeno:			
type 1	5	0	0
type 2	2(+1)	3(+)	3(+2)
type 3	2	3	3
type 5	—	3(+1)	5(+1)
type 6	1	—	1
type 7	1	4(+1)	4(+1)
untyped	—	5(+1)	4(+1)
Coxsackie B:			
type 2	1	1	1
type 5	2	2	2
ECHO 9	1	2	2
Herpes simplex	1(+1)	1(+2)	1(+3)
Total	40(+2)	82(+7)	84(+7)

Figures in parentheses indicate double infections with RS or parainfluenza viruses, which were considered to be the main etiologic agent.
The other 2 double infections with adenovirus type 7.

in detail elsewhere (29). One isolation of parainfluenza virus type 3 was considered significant even though the convalescent phase serum specimen was not available because the isolation was obtained during a parainfluenza virus type 3 outbreak.

Following the procedure of Berglund (7) the RS virus was isolated from the middle ear exudates of 5 infants with otitis media during the RS virus outbreaks. These studies have been described in detail earlier (29).

Infants of the family group. The results of relevant virus isolations and antibody rises are shown in Table 6. From the 208 acute respiratory illnesses 55 virus strains were isolated, but the number of significant isolations was 46 (22.0 per cent positive).

One RS virus isolation without antibody rise was considered adequate for identification because the convalescent phase serum specimen was taken relatively soon after the onset of the illness. This was also the case in one isolation of parainfluenza type 3. The isolation of adenovirus type 6 shown in Table 5 was only confirmed by a significant rise in the CF test. Six sporadic isolations of adenoviruses and one of herpes simplex virus were not followed by an antibody rise.

Children of the family group aged 2-6 years. The results of the relevant virus isolations and antibody rises are given in Table 7.

The 106 acute respiratory illnesses of this group yielded 30 virus isolates, 26 of which were considered significant (4.6 per cent positive).

Table 7. *Virus etiology of the 106 acute respiratory ill cases in the children of the family group aged 2-6 years*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	0	13	13
Parainfluenza			
type 2	—	4	4
untyped	1**	2**	3
Influenza A2	4	3	8
Adeno			
type 1	2	3	3
type 2	1	4	4
type 3	2	2	2
type 5	0	3	3
type 6	1	1	2
type 7	2	3	3
Coxsackie B			
type 3	3	4	4
ECHO 9	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	26	50(+1)	30(+1)

Figure 1a parenthesis indicates double infection with adenovirus type 6.
The isolate, positive in hemadsorption but low hemagglutinating activity and could not be passaged, the paired sera yielded equal rises to parainfluenza types 1 and 3 in CF and HI tests.

and family groups ($p = 0.001$ chi-square test). The differences between the infants and the children aged 2-6 years in the family group were not statistically significant.

Infants of the nursery group. The results of relevant virus isolations and antibody rises in the 188 acute respiratory illnesses in the infants of the nursery group are given in Table 5.

Of the original 57 pharyngeal and 16 rectal isolates, only 33 from pharyngeal and 2 from rectal swabs were considered to be etiologic agents (18.6 per cent positive). Fourteen adenovirus strains were detected in both pharyngeal and rectal swabs on the same

occasion and treated as a single isolation. In 8 cases of virus isolation there was presumptive evidence that the Coxsackie B type and adenoviruses isolated were not etiologic agents in the current illnesses, because the virus had been isolated earlier or a significant serologic rise to the type had occurred earlier. Adenovirus types 1, 2 and 5 not followed by an antibody rise were isolated from 11 infants; in 3 cases RS or parainfluenza virus infections were simultaneously detected. One third of these adenovirus isolations were sporadic.

The virus isolations and serologic results of the RS virus outbreak have been described

Table II *Virus etiology of the 208 acute respiratory illnesses in the infants of the family group*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	13	4	23
Parainfluenza:			
type 1	4	6	6
type 2	1	3	3
type 3	4	8	9
untyped	3	5	5
Influenza A2	3	4	4
Adeno:			
type 1	5	6	6
type 2	3(+1)	3(+)	3(+)
type 3	2	3	3
type 5	2	3(+1)	5(+1)
type 6	1	—	1
type 7	1	4(+1)	4(+1)
untyped	—	3(+1)	4(+1)
Coxsackie B			
type 1	1	1	1
type 3		2	
ECHO 9	1	2	3
Herpes simplex	1(+1)	1(+2)	1(+)
Total	46(+2)	82(+7)	84(+7)

Figures in parentheses indicate double infections with RS or parainfluenza viruses, which were considered to be the main etiologic agents.
The other 2 double infections with adenovirus type 7

viruses and 3 of herpes simplex virus were not followed by antibody responses.

In the group of oldest family children only one significant serologic rise to Coxsackie B type was observed and no viruses were isolated.

Parents of the family group The results of the relevant virus isolations and antibody rises are shown in Table 9. From the observed 34 cases of illness 5 viruses were isolated. One adenovirus isolation was not followed by an antibody rise.

In the family group the total number of acute respiratory illnesses with identified viral etiology was 162 in the 410 illnesses studied (39.5 per cent positive). The number of significant antibody rises was 168 (38.8 per cent positive) and the number of etiologically relevant virus isolations 86 (20.7 per cent). In 11 cases a double infection was detected.

IDENTIFIED VIRUS INFECTIONS

In Fig 3 the monthly frequency of acute respiratory illnesses with identified viral etiol

ogy with respect to the total monthly number of illnesses observed is presented. In almost every month some acute respiratory illnesses were diagnosed virologically but only on a few occasions was a high percentage of diagnosed illnesses recorded.

RS virus infections

As already stated, all evidence of RS virus infection was considered to be etiologically significant. No infections with RS virus were observed among oldest children and parents.

In Fig 4 the prevalence of RS infection is shown. In the families the RS infections occurred in two outbreaks, in the first 28 per cent of the infants contracted it, and in the second the attack rate was 25 per cent in both infants and children aged 1-6 years.

In the nursery group only one outbreak of RS virus infections occurred, when all the infants contracted it. This outbreak has been described in detail in connection with the studies of RS virus in the middle ear exudates

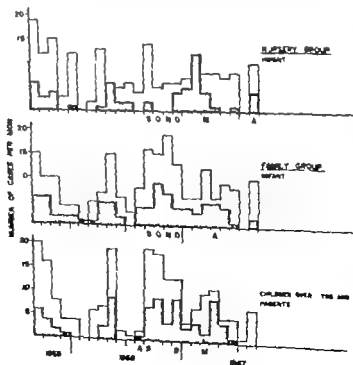


Fig 3. The number of acute respiratory illnesses with identified viral etiology (shaded) and the total monthly number of illnesses studied.

Table 8 Virus etiology of the 55 acute respiratory illnesses in the school-children of 1 family group aged 7-10 years

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	—	0	0
Parainfluenza			
type 2	3	3	
type 3	1		
untyped	—	1	1
Influenza A ₂		1	1
Adeno:			
type 1	1	1(+1)	1(+1)
type 3	2	3	3
type 7	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	9	10(+2)	20(+2)

Figures in parentheses indicate double infections with influenza A₂ and RS viruses, which were considered to be the main etiologic agents.

Equal rises in parainfluenza types 1 and 3 antibodies in CF and HI tests.

Two isolations of adenoviruses and two of herpes simplex virus were not followed by an antibody rise.

School-children of the family group The results of the relevant virus isolations and antibody rises in the school-children aged 7-10 years are shown in Table 8.

From the 55 cases of acute respiratory illness reported 14 virus isolates were obtained. One influenza A₂ virus isolation without antibody rise was considered to be significant because the CF and HI antibody titers were already very high in the acute phase specimen. Two isolations of adeno-

Table 9 Virus etiology of the 31 acute respiratory illnesses in the parents of the family group

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
Parainfluenza			
type 3	—	1	1
Influenza A ₂	1		1
Adeno			
type 1	2	2	2
ECHO 9	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	4	7(+1)	7(+1)

Figure in parentheses indicates a double infection with adenovirus type 1.

infections occurred and only one infection with parainfluenza virus type 3 was observed in the parents.

In Fig. 8 the parainfluenza virus infections of the infants and children are shown. At the time when the parainfluenza virus type 3 outbreak occurred in the nursery when 50 per cent of the infants contracted it, the same type was prevalent among the family infants and children, with an attack rate of approximately 90 per cent. Sporadic cases of parainfluenza virus infection occurred in the family group in the fall and spring seasons. In March and May 1967 several cases of illness due to parainfluenza virus types 1 and 2 were observed in the infants of the family group.

In the nursery the infection rate of parainfluenza virus was 0.23 per person year. In the family infants the infection rate was 0.26 per person-year the same as observed among the nursery infants. The rates of parainfluenza virus infection were 0.08 per person-year in children aged 2-6 years and 0.03 in school children of the family group.

Influenza A2 virus infections

No cases of influenza A₂ infection were seen in the nursery. In the family group, no sporadic infection with influenza A₂ was observed in September 1968, but in April-May 1967 family outbreaks occurred. The infection spread within 4 families (10.5 per cent of the families under observation) and was experienced by 14 individuals (Fig. 6).

Adenovirus infections

Infection rate Infections indicated by the first isolation of an adenovirus without detectable antibody response were also included. In the nursery group 51 adenovirus infections occurred, in the infants of the family group 31 in the children aged 2-6 years 19 in school-children and parents 10 infections.

Fig. 7 shows the cumulative adenovirus infection rates and the appropriate cases in the study groups.

The prevalence of adenovirus infections was highest in the infants of the nursery group 1.7 per person year. In the infants of the family group the rate was 0.4 in children aged 2-6 years 0.3 and in school-children only 0.1 per person year. The adenovirus infection rate in the nursery was 4-fold that observed in the infants of the family group.

Adenovirus types. The commonest types were 1 and 5. The distribution of adenovirus types in the illnesses with adenovirus etiology in the younger children is shown in Tables 5, 6 and 7. There are no significant differences between the groups.

In Fig. 8 the occurrence of the adenovirus types 1 and 5 among the infants is shown. Adenovirus type 1 reached an infection rate of 0.5 per person year in the nursery group while it was only 0.08 per person year in the infants of the family group. Thus, compared to the rate observed in the infants of the family group, the rate in the nursery was 3-fold. The infections with type 1 were sporadic.

In the infants of the nursery group, the infection rate of adenovirus type 2 was 0.5

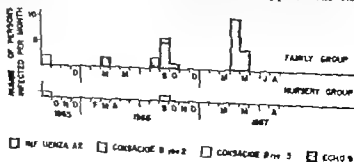


Fig. 6. Influenza A2 and enterovirus infections.

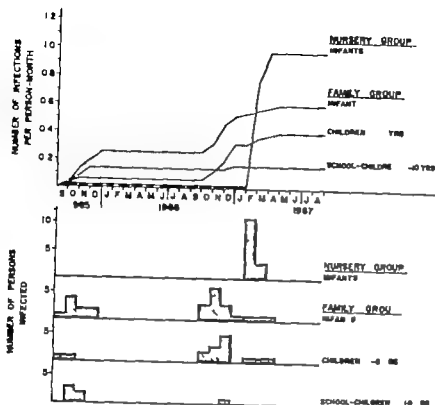


Fig 4. RS virus infections. Cumulative rate of RS infections and the cases observed.

of infants with otitis media published elsewhere (29).

In the nursery group infants the RS virus infection rate was 0.5 per person year. In the infants of the family group the rate was 0.3 per person year. In the nursery infants the rate exceeded that found in the family infants by 1.7 fold. In the family group children aged 2-6 years had an RS infection rate of 0.2 per person year and the school

children a rate of 0.1 per person year. The double infections of RS virus and some other virus were described in a previous section.

Parainfluenza virus infections

All the parainfluenza virus infections detected were considered to be etiologically significant. In the oldest children no parainfluenza virus

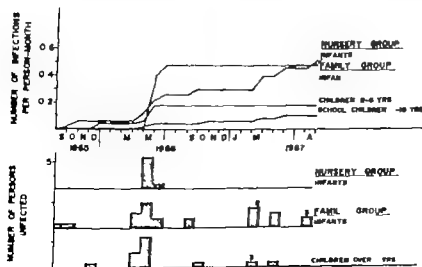


Fig 5. Parainfluenza virus infections. Cumulative rate of parainfluenza virus infections and the cases observed. The numbers in the bar diagram indicate the type of the parainfluenza virus.

infections occurred and only one infection with parainfluenza virus type 3 was observed in the parents.

In Fig. 6 the parainfluenza virus infections of the infants and children are shown. At the time when the parainfluenza virus type 3 outbreak occurred in the nursery when 50 per cent of the infants contracted it, the same type was prevalent among the family infants and children, with an attack rate of approximately 20 per cent. Sporadic cases of parainfluenza virus infection occurred in the family group in the fall and spring seasons. In March and May 1967 several cases of illness due to parainfluenza virus types 1 and 2 were observed in the infants of the family group.

In the nursery the infection rate of parainfluenza virus was 0.23 per person year. In the family infants the infection rate was 0.26 per person year the same as observed among the nursery infants. The rates of parainfluenza virus infection were 0.08 per person-year in children aged 1-6 years and 0.05 in school children of the family group.

Influenza A2 virus infections

A case of influenza A2 infection was seen in the nursery. In the family group one sporadic infection with influenza A2 was observed in September 1966, but in April-May 1967 family outbreaks occurred. The infection spread within 4 families (10.8 per cent of the families under observation) and was experienced by 14 individuals (Fig. 6).

Adenovirus infections

Infection rate Infections indicated by the first isolation of an adenovirus without detectable antibody response were also included. In the nursery group 51 adenovirus infections occurred, in the infants of the family group 31 in the children aged 1-6 years 19 in school-children and parents 10 infections.

Fig. 7 shows the cumulative adenovirus infection rates and the appropriate cases in the study groups.

The prevalence of adenovirus infections was highest in the infants of the nursery group 1.7 per person year in the infants of the family group the rate was 0.4 in children aged 1-6 years 0.3 and in school-children only 0.1 per person year. The adenovirus infection rate in the nursery was 4-fold that observed in the infants of the family group.

Adenovirus types. The commonest types were 1 and 5. The distribution of adenovirus types in the illnesses with adenovirus etiology in the younger children is shown in Tables 6, 6 and 7. There are no significant differences between the groups.

In Fig. 8 the occurrences of the adenovirus types 1 and 5 among the infants is shown. Adenovirus type 1 reached an infection rate of 0.23 per person year in the nursery group while it was only 0.06 per person-year in the infants of the family group. Thus, compared to the rate observed in the infants of the family group, the rate in the nursery was 3-fold. The infections with type 1 were sporadic.

In the infants of the nursery group, the infection rate of adenovirus type 5 was 0.5

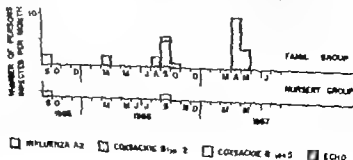


Fig. 8. Influenza A2 and adenovirus infections.

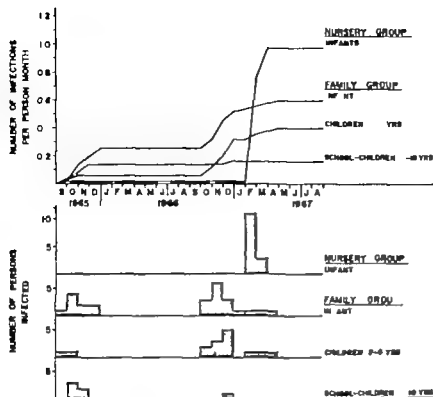


Fig 4. RS virus infections. Cumulative rate of RS infections and the cases observed.

of infants with otitis media published elsewhere (29)

In the nursery group infants the RS virus infection rate was 0.5 per person year. In the infants of the family group the rate was 0.3 per person year. In the nursery infants the rate exceeded that found in the family infants by 17 fold. In the family group children aged 2-6 years had an RS infection rate of 0.2 per person year and the school

children a rate of 0.1 per person year. The double infections of RS virus and some other virus were described in a previous section.

Parainfluenza virus infections

All the parainfluenza virus infections detected were considered to be etiologically significant. In the oldest children no parainfluenza virus

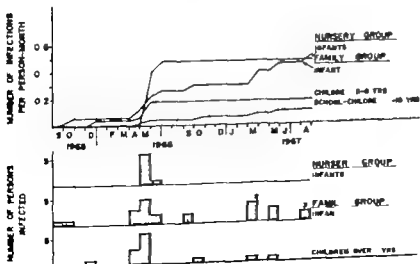


Fig 5. Parainfluenza virus infections. Cumulative rate of parainfluenza virus infections and the cases observed. The numbers in the bar diagram indicate the type of the parainfluenza virus.

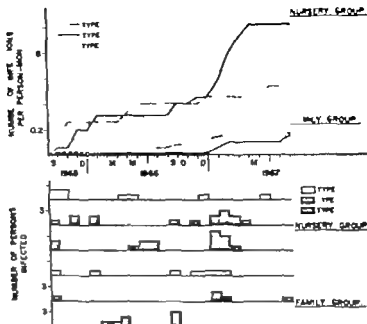


Fig. 8 Infections with adenovirus types 1, 2 and 5 among the family. Cumulative infection rates and the cases observed in the infants of the nursery and family groups.

(Fig. 6) In March 1966 a mother and daughter and in August 1966 twin brothers contracted this infection

Herpes simplex infections

In one infant herpes simplex virus was the only etiologic agent detected. All the other infections with herpes simplex were observed in connection with infections with other viruses. All the cases were sporadic.

Comparison of outbreaks with identified virus etiology and outbreaks of unknown etiology

The outbreaks were presented in Fig. 9.

The etiologic agents in the observed outbreaks of acute respiratory illness were the following:

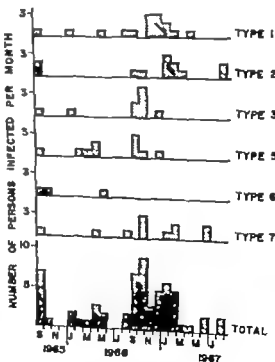


Fig. 9 Adenovirus types 1-7 associated with respiratory illnesses of adenovirus etiology in the family group.

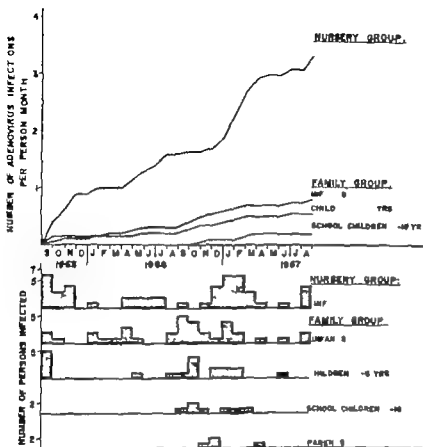


Fig 7 Adenovirus infection rates. Comparative rate of adenovirus infections and the cases observed.

per person year. In the infants of the family group the rate was only 1/6th, 0.08 per person year.

The infection rate of type 5 was as high as the rate of type 3 in the infants of the nursery group 0.5 per person year. The prevalence of type 5 among the family infants was of a low order 0.08 per person year.

The adenovirus types 2 and 5 each comprised one-third of the adenovirus infections in the nursery, but among the infants of the family group types 1, 2, and 5 were equally frequent.

In August 1967, 4 cases of CF rises to adenovirus antibodies were observed in the nursery, one of these with isolation of an adenovirus. These could not be proved to belong to the types 1-7 tested.

In Fig 9 the illnesses with adenovirus etiology in the families are shown. Summarizing among the families types 1, 2, 3, and 5 occurred

in small outbreaks, type 7 sporadically and only 3 cases of type 6 infection were detected.

Enterovirus infections

An outbreak of respiratory illness associated with Coxsackie B type 2 infection was observed in the families in September-October 1966 (Fig 6). The cases observed were from 4 families. In addition 2 children in a fifth family showed high antibody titers to this virus, but no rise was demonstrated.

In September 1967 a few Coxsackie B type 5 infections were observed simultaneously in the infants of the nursery and family groups (Fig 6). One sporadic case of Coxsackie B type 5 infection was observed in the nursery in September 1966.

In the family group 4 infections with Picornavirus were detected in two families.

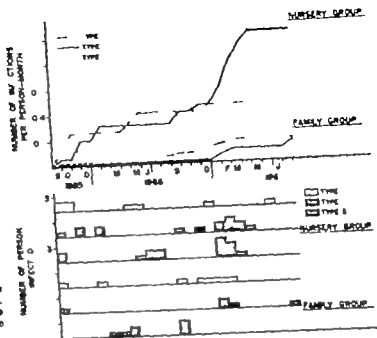


Fig. 8. Infections with adenovirus types 1, 2 and 6 among the infants. Cumulative infection rates and the cases observed in the infants of the nursery and family groups.

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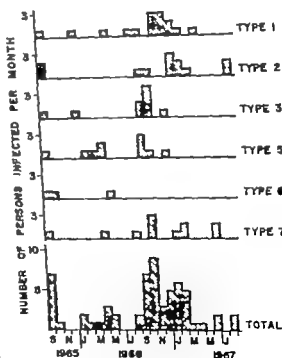


Fig. 9. Adenovirus types 1-7 associated with respiratory illness of adenovirus etiology in the family group.

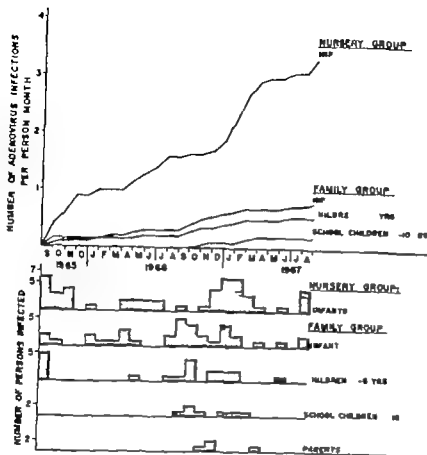


Fig. 7. Adenovirus infections. Cumulative rate of adenovirus infection and the cases observed.

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In September 1966, a few Coxsackie B type 5 infections were observed simultaneously in the infants of the nursery and family groups (Fig. 6). One sporadic case of Coxsackie B type 5 infection was observed in the nursery in September 1966.

In the family group 4 infections with FC/HO 9 virus were detected in two families.

Other children of the family group

Children aged 1-6 years

Outbreaks of respiratory illness	Etiologic agents
1965 September	adenoviruses
October	RS virus, unknown
1966 March-April	unknown
May	parainfluenza virus type 3
September	Coxsackie B type 2, unknown
October	adenoviruses, RS virus
November	RS virus
December	RS virus
1967 April	influenza A ₂ virus
June-July	unknown

In 2 of the 10 outbreaks the etiology was wholly obscure, 4 were associated with infection by a single virus (Figures 4-6) and the others were due to infections with several viruses.

In the school-children aged 7-10 three outbreaks of illness were observed: the first was associated with parainfluenza virus type 3 infection. In the other outbreaks the etiologic agents were not identified.

In the infants of the nursery group and of the family group the outbreaks of respiratory illnesses with specific virus etiology corresponded only in September 1965 (adenoviruses, Coxsackie B type 5) and May 1966 (parainfluenza virus type 3). In five simultaneously occurring outbreaks the etiology remained totally or partially obscure.

CLINICAL OBSERVATIONS

Clinical diagnosis of acute respiratory illness

Distribution of all cases to upper and lower respiratory tract infections. The term upper respiratory illness (URI) includes the illnesses with symptoms from nose to trachea. Similarly lower respiratory illness (LRI) includes

all illnesses with involvement of the lower respiratory tract.

In Table 10 the clinical diagnoses in the acute respiratory illnesses with detected virus etiology and with unknown etiology are shown. In addition, in the nursery infants two cases of URI were associated with a Coxsackie B type 5 infection. In the family infants 7 cases of URI were associated with influenza A₂, Coxsackie B type 5, ECHO virus type 9 and herpes simplex virus infections, and in three cases of bronchitis influenza A₂, Coxsackie B virus type 2 and 5 were the etiologic agents.

The ratios of URI to LRI were compared by the chi-square test. Among the infants of the nursery group there was a highly significant difference between the ratios for the illnesses with detected virus etiology and those of unknown etiology. Among the infants of the family group there was no such difference. Between the infants of the nursery and family groups the ratios differed significantly among the illnesses of unknown etiology but not among the illnesses with detected virus etiology.

Even the illnesses with detected virus etiology were more often mild in the older children.

Infants of the nursery group

Outbreaks of respiratory illness . . . Etiologic agents

1965	September	adenovirus types 1 5 Coxsackie B type 5 unknown
	October	adenovirus types 1 6 unknown
	November	adenovirus types 2, 6 unknown
1966	January—February	unknown
	April	unknown
	May	parainfluenza virus type 3
	June—July	adenovirus type 5 unknown
	August—September	unknown
	October—November	unknown
	December	adenovirus type 7
1967	January	adenovirus types 5 2
	February—March	RS virus
	April—May	unknown
	June	unknown
	August	untyped adenovirus, unknown

Among the 15 major outbreaks of acute respiratory illness, the etiology was not established in 5 4 outbreaks were associated with parainfluenza virus type 3 adenovirus established in 6 and was only partially or RS virus (Figures 5 7 9 and 4)

Infants of the family group

Outbreaks of respiratory illness . . . Etiologic agents

1965	September	adenovirus, Coxsackie B type 5 RS virus
	October	RS virus
	November	unknown
1966	April	parainfluenza virus type 3 adenovirus type 5
	May	parainfluenza virus type 3 unknown
	June	unknown
	July—August	unknown
	September	adenovirus, parainfluenza virus type 1 unknown
	October	adenovirus, RS virus, Coxsackie B type 2
1967	November	RS virus, unknown
	December	RS virus, unknown
	March	parainfluenza virus type 1 2
	April	influenza virus A2
	May	parainfluenza virus type 1
	June—July	unknown
	August	unknown parainfluenza virus type 3

In 4 of the 16 outbreaks the etiology remained wholly obscure and in 5 it was only partially clarified. In 4 of the outbreaks several viruses were together responsible for the outbreak. Three outbreaks were associated with RS, parainfluenza and influenza viruses (Figures 4—6)

Other children of the family group

Children aged 1—6 years

Outbreaks of respiratory illness	Etiologic agents
1965 September	adenoviruses
October	RS virus, unknown
1966 March—April	unknown
May	parainfluenza virus type 3
September	Coxsackie B type 5, unknown
October	adenoviruses, RS virus
November	RS virus
December	RS virus
1967 April	influenza A ₁ virus
June—July	unknown

In 10 of the 10 outbreaks the etiology was wholly obscure, 4 were associated with infection by a single virus (Figures 4—6) and the others were due to infections with several viruses.

In the school-children aged 7—10 three outbreaks of illness were observed the first was associated with parainfluenza virus type 3 infection. In the other outbreaks the etiologic agents were not identified.

In the infants of the nursery group and of the family group the outbreaks of respiratory illnesses with specific virus etiology corresponded only in September 1965 (adenoviruses, Coxsackie B type 5) and May 1966 (parainfluenza virus type 3). In five simultaneously occurring outbreaks the etiology remained totally or partially obscure.

CLINICAL OBSERVATIONS

Clinical diagnosis of acute respiratory illness

Distribution of illnesses to upper and lower respiratory tract infections. The term upper respiratory illness (URI) includes the illnesses with symptoms from nose to trachea. Similarly lower respiratory illness (LRI) includes

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In Table 10 the clinical diagnoses in the acute respiratory illnesses with detected virus etiology and with unknown etiology are shown. In addition to the nursery infants two cases of URI were associated with a Coxsackie B type 5 infection. In the family infants 7 cases of URI were associated with influenza A₁, Coxsackie B type 5, ECHO virus type 9 and herpes simplex virus infections, and in three cases of bronchitis influenza A₁, Coxsackie B virus type 5 and 5 were the etiologic agents.

The ratios of URI to LRI were compared by the chi-square test. Among the infants of the nursery group there was a highly significant difference between the ratios for the illnesses with detected virus etiology and those of unknown etiology. Among the infants of the family group there was no such difference. Between the infants of the nursery and family groups the ratios differed significantly among the illnesses of unknown etiology but not among the illnesses with detected virus etiology.

Even the illnesses with detected virus etiology were more often mild in the older children.

Table 10 Clinical diagnosis of the acute respiratory illnesses

Illnesses	Illnesses with detected virus etiology										Illnesses of unknown etiology									
	Nursery group					Family group					Nursery group					Family group				
	Infant					Infant					Children --0 yrs members					Children --0 yrs members				
	Total					Total					Total					Total				
	EB	Infant	Adm	Other	No.	EB	Infant	Adm	Other	No.	EB	Infant	Adm	Other	No.	EB	Infant	Adm	Other	No.
URI	4	30	2	—	36	13	1	22	7	44	4	119	91	53	64	—	—	—	—	—
(roup	—	—	—	—	—	—	7	—	—	11	6	—	0	—	4	—	—	—	—	—
bronchitis	7	3	0	—	10	0	4	3	15	4	—	10	90	3	—	—	—	—	—	—
bro chiolitis	3	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
pneumonia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total number of illnesses	14	7	23	—	68	—	27	0	10	84	50	130	14	56	68	—	—	—	—	—

In the nursery group the differences in proportions of URI and bronchitis between the RS, parainfluenza and adenovirus groups were very highly significant (chi-square test). In the family infants among the RS, parainfluenza and adenovirus infections the difference was less significant ($p < 0.05$). When the distributions of diagnosis in each virus group were compared with the corresponding distribution in the other infant group no significant differences could be observed.

Clinical conditions requiring hospitalization. During the RS virus outbreak in the nursery 4 infants were sent to hospitals with clinical diagnoses of bronchitis, bronchiolitis and broncho-pneumonia (29). In addition, one baby with pneumonia of unknown etiology was hospitalized in December 1965.

One infant in the family group was twice sent to hospital with pneumonia, which on one of these occasions was associated with RS virus infection. No other admissions because of respiratory illnesses occurred during the study period.

Signs and symptoms

The most frequent signs and symptoms in the acute respiratory illnesses observed are shown in Table 11. The distributions in the frequencies of the signs and symptoms were compared by the chi-square test. Among the infants of the nursery group the difference in the frequencies between illnesses with detected virus and unknown etiology was highly significant, but among the other groups the differences were not significant. Among the illnesses with detected virus etiology between the infants of the nursery and family groups the difference in the frequencies was significant but it was highly significant among the illnesses with unknown etiology.

Sore throat was more common in the older members of the family group than in the

Table 1) Commonly observed signs and symptoms in infants with illness of unknown etiology

Signs and symptoms	Infants with detected virus etiology				Infants with unknown etiology			
	Nursery group		Family group		Nursery group		Family group	
	Infants (23 illnesses)	Infants (84 illnesses)	Children 2-3 yrs (40 illnesses)	Other children (25 illnesses)	Infants (120 illnesses)	Infants (14 illnesses)	Children 2-3 yrs (24 illnesses)	Other children (66 illnesses)
Diarrhea	10	9	100	100	96	100	98	97
Cough	100	99	91	91	100	99	99	97
Hoarse throat	86	99	8	26	1	1	7	57
Infected pharynx	84	91	94	94	73	73	60	62
Hoarse voice	2	50	8	11	4	10	12	20
Rhinitis	23	19	9	7	8	22	7	9
General bronchopulmonary illness	23	26	1	29	7	29	27	22
Otitis media	23	21	6	—	6	15	4	—
Generalized symptoms	2	8	14	7	7	10	4	0

children aged 2-8 years (in illnesses with detected virus etiology $p < 0.01$, in illnesses of unknown etiology $p < 0.001$ t-test) Rhonchi were observed more often in the nursery group infants in illnesses with detected virus etiology ($p < 0.01$ t-test). The same significant difference was observed in the occurrence of otitis media in illnesses with detected virus etiology and of unknown etiology among the infants of the nursery group.

In addition, rales were observed in 9 infants in the nursery one of these had an RS virus infection. Expiratory wheezing was present in 5 infants with RS virus infection who also had general symptoms of the bronchiolitis syndrome (29). Conjunctivitis was observed in only one infant with an adenovirus infection and in two with illness of unknown etiology.

In the infants of the family group lymphadenitis was observed in 11 out of 23 parainfluenza virus infections and 9 out of 26 adenovirus infections, and otitis media in 9 out of 26 RS and 6 out of 23 parainfluenza virus infection. Signs of bronchiolitis were observed in 5 infants with RS virus infection and one with parainfluenza virus infection. Rales were heard in two infants with RS virus infection and in one with illness of unknown etiology. Conjunctivitis was observed in 5 infants with adenovirus, RS and parainfluenza virus infections and in 6 infants with illness of unknown etiology.

Fever

Prevalence of fever The results of the temperature readings were divided into three classes according to the highest temperature observed.

No fever	temperature $\leq 37.5^{\circ}\text{C}$
Low fever	temperature $= 37.6 - 38.5^{\circ}\text{C}$
High fever	temperature $\geq 38.6^{\circ}\text{C}$

Table 10 Clinical diagnosis of the acute respiratory illnesses

Illnesses	Illnesses with detected virus etiology										Ill cases of unknown etiology				
	Nursery group					Family group					Nursery group		Family group		
	Infants					Infants					Infants		Children 0-6 yrs members		
	RS	Para influenza	Adeno	Other	Total	RS	Para influenza	Adeno	Other	Total	Infants	Children 0-6 yrs members	Other	Children 0-6 yrs members	
URI	2	4	30	2	38	13	12	23	7	54	41	24	119	91	64
Group	—	—	—	—	—	—	7	—	—	11	5	2	—	6	4
Bronchitis	7	3	5	—	15	6	4	3	3	16	4	2	10	20	3
Bronchiolitis	3	—	—	—	3	—	—	—	—	2	—	—	—	—	—
Pneumonia	—	—	—	—	2	—	—	—	—	2	—	—	1	1	—
Total number of illnesses	14	7	35	2	58	3	23	20	10	84	50	28	130	124	68

In the nursery group the differences in proportions of URI and bronchitis between the RS parainfluenza and adenovirus groups were very highly significant (chi-square test). In the family infants among the RS, parainfluenza and adenovirus infections the difference was less significant ($p < 0.05$). When the distributions of diagnoses in each virus group were compared with the corresponding distribution in the other infant group no significant differences could be observed.

Clinical conditions requiring hospitalization. During the RS virus outbreak in the nursery 4 infants were sent to hospitals with clinical diagnoses of bronchitis, bronchiolitis and broncho-pneumonia (29). In addition one baby with pneumonia of unknown etiology was hospitalized in December 1965.

One infant in the family group was twice sent to hospital with pneumonia, which on one of these occasions was associated with RS virus infection. No other admissions because of respiratory illnesses occurred during the study period.

Signs and symptoms

The most frequent signs and symptoms in the acute respiratory illnesses observed are shown in Table 11. The distributions in the frequencies of the signs and symptoms were compared by the chi-square test. Among the infants of the nursery group the difference in the frequencies between illnesses with detected virus and unknown etiology was highly significant, but among the other groups the differences were not significant. Among the illnesses with detected virus etiology between the infants of the nursery and family groups the difference in the frequencies was significant but it was highly significant among the illnesses with unknown etiology.

Sore throat was more common in the older members of the family group than in the

duration of fever in the nursery group infants were 3 days in the febrile illnesses both with detected virus etiology and of unknown etiology. The longest episode of fever lasting 7 days, occurred in an infant with an RS virus infection. In the infants of the family group the mean and median duration of fever were 3 days in both illnesses due to RS virus infection was the same 3 days. In the infants of the family group the fever persisted for a mean of 4 days in influenza A2 infections, and the longest fever episodes, 7 days and 6 days were observed in an adenovirus infection and one illness of unknown etiology.

In the family children aged 2-6 years the mean duration of fever was 3 days in febrile illnesses with detected virus etiology and 4 days in illnesses of unknown etiology. The mean duration of fever in the influenza A2 infections was 4 days. The number of febrile illnesses among other members of the families was low.

Duration of the acute respiratory illnesses

In many illnesses, particularly in the infant groups, the duration of illness was due to the persistence of nasal discharge. The mean durations of respiratory illnesses are shown in Table 13.

The mean duration of illnesses with detected virus etiology and of unknown etiology was highly significantly longer in the infants of the nursery group than in those of the family group (*t*-test). In the infants of the family group the illnesses with detected virus etiology lasted longer than the corresponding illnesses in children aged 2-6 years ($p < 0.001$ *t*-test).

In the infants in the nursery group the duration of illnesses due to RS and adenovirus infections was longer than in the infants in the family group ($p < 0.05$, *t*-test).

OTHER ILLNESSES

Only respiratory illnesses were examined and information about other infections was later obtained from the personnel in the nursery and the mothers of the families. No specimens were taken during these illnesses.

In the nursery an epidemic of rubella occurred in March 1966, when half of the infants contracted rubella. Episodes of fever without other symptoms were observed in four infants. In addition, 3 infants had diarrhoea and 2 cases of bacterial tonsillitis occurred.

In the infants of the family group 8 cases of rubella, 8 cases of varicella, 11 cases of measles and 2 cases of mumps occurred. Febrile episodes without other symptoms were observed in 8 infants. Diarrhoea was reported

Table 13 Mean duration of acute respiratory illnesses: days

Etiology of illness	Nursery group		Family group	
	Infants	Infants	Children 2-6 yrs	Other members
Detected virus etiology	19	14	10	10
RS virus infections	19	14	10	11
Parainfluenza virus infection	18	12	9	10
Adenovirus infections	19	13	10	8
Unknown etiology	19	12	11	8

The occurrence of fever in the acute respiratory illnesses is shown in Table 12.

The frequency of fever in the illnesses was compared by the chi-square test. Among the infants of the nursery group between the illnesses with detected virus etiology and those of unknown etiology the difference in the occurrence of fever was almost significant but it was highly significant among the infants of the family group. Both among the illnesses with detected virus etiology and also in the illnesses of unknown etiology the difference in the frequency of fever between the infants of the nursery and those of the family group was highly significant.

In the adenovirus infections, the difference in the frequency of fever between the infants of the nursery and family groups was highly significant. In the infants of the family group all infections with adenovirus types 1, 2, 3 and 7 and even some of the type 5 infections were febrile, whereas of the infants of the nursery group only a few with type 5 infections were febrile. Of the adenovirus illnesses without fever in the infants of the nursery group 10 occurred in infants aged less than 6 months and in the family group 2 occurred in infants as young as this. No febrile cases of adenovirus infections were observed in infants aged less than 8 months in the family group but two occurred in 5-month-old infants in the nursery group. Among the infants of the nursery group between the illnesses due to RS parainfluenza and adenovirus the difference in the occurrence of fever was highly significant.

In the family group the occurrence of fever in the illnesses of other children was similar to the occurrence observed in the infants. All the influenza A2 virus infections in the family infants were febrile and only 3 of the 11 influenza A2 infections in the older family members were not febrile. Among the older members a half of the adenovirus and RS virus infections were febrile.

Duration of fever The mean and median

Table 12. Fever in the acute respiratory illnesses

Fever	Illnesses with detected virus etiology										Illnesses of unknown etiology			
	Nursery group					Family group					Nursery group		Family group	
	Infants					Infants					Children 2-6 yrs members		Children 6-12 yrs members	
	RS	P re-influenza	Adeno	Other	Total	RS	P re-influenza	Adeno	Other	Total	Children 2-6 yrs members	Total	Infants	Other
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
No	3	2	29	2	36	0	6	5	1	12	15	14	105	63
Low	6	2	4	—	12	0	8	5	2	1	16	8	10	28
High	3	3	2	—	10	13	9	10	7	45	19	6	14	33
Total number of illnesses	14	7	34	2	53	25	23	29	10	64	60	28	130	91

durations of fever in the nursery group infants were days in the febrile illnesses both with detected virus etiology and of unknown etiology. The longest episode of fever, lasting 7 days, occurred in an infant with an RS virus infection. In the infants of the family group the mean and median duration of fever were 3 days in both illnesses groups. Also in the infants of the nursery group the duration of fever in illnesses due to RS virus infection was the same 3 days. In the infants of the family group the fever persisted for a mean of 4 days in influenza A₁ infections, and the longest fever (episodes, 7 days and 6 days were observed in an adenovirus infection and one illness of unknown etiology).

In the family children aged 2-6 years the mean duration of fever was 3 days in febrile illnesses with detected virus etiology and 2 days in illnesses of unknown etiology. The mean duration of fever in the influenza A₁ infections was 4 days. The number of febrile illnesses among other members of the families was low.

Duration of the acute respiratory illnesses

In many illnesses, particularly in the infant groups, the duration of illness was due to the persistence of nasal discharge. The mean durations of respiratory illnesses are shown in Table 13.

The mean duration of illnesses with detected virus etiology and of unknown etiology was highly significantly longer in the infants of the nursery group than in those of the family group (t-test). In the infants of the family group the illnesses with detected virus etiology lasted longer than the corresponding illnesses in children aged 2-6 years ($p < 0.001$ t-test).

In the infants in the nursery group the duration of illnesses due to RS and adenovirus infections was longer than in the infants in the family group ($p < 0.05$ t-test).

OTHER ILLNESSES

Only respiratory illnesses were examined and information about other infections was later obtained from the personnel in the nursery and the mothers of the families. No specimens were taken during these illnesses.

In the nursery an epidemic of rubella occurred in March 1966, when half of the infants contracted rubella. Episodes of fever without other symptoms were observed in four infants. In addition, 3 infants had diarrhea and 2 cases of bacterial tonsillitis occurred.

In the infants of the family group 8 cases of rubella, 8 cases of varicella, 11 cases of measles and 3 cases of mumps occurred. Febrile episodes without other symptoms were observed in 8 infants. Diarrhea was reported

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Adenovirus infections	19	13	III	8
Unknown etiology	19	12	11	8

from 18 infants, while bacterial tonsillitis and otitis media without respiratory symptoms were observed in 3 infants.

In the children aged 2—6 years 29 episodes of communicable diseases of childhood were reported, 13 measles, 9 varicella 5 rubella and 2 cases of mumps. Diarrhea occurred in 10 children

In the group of school-children the number of communicable diseases was 33, measles occurred in 13 children varicella in 8, rubella in 5 mumps in 6 and scarlet fever in one. These communicable diseases of childhood did not occur in major epidemics, although most of the cases were seen in the spring and fall.

Discussion

In this investigation two different groups of infants were compared. The ages of the infants differed, but it was considered impossible to maintain the mean age of the infants in the family group on the level of the infants in the nursery group. This would have been possible only with constant recruitment and release of the families. The main activity of the nursery was to provide temporary care of infants, and consequently there was only a relatively short mean observation period per infant. The number of the infants in the groups also differed. However whenever a viral agent invaded the nursery the opportunity to detect the infections was relatively good because of the close watch kept over the infants. Of the 2800 families with 3 or more children in the city the number of families under surveillance comprised 17 per cent at the most. It was felt however that the group of family infants was large enough to reflect the epidemics of acute respiratory disease in the city. This was further ensured by selection of families living in different areas and by the study of the acute respiratory illnesses in the siblings and parents in the families.

The study procedure was laborious and required adaptation on the part of the families, both mothers and children. Taking the children to the outpatient clinic itself was a great inconvenience to the mothers. It is understandable that some minor illnesses were missed. Difficulties in cooperation were encountered, especially with the families in which proper care was not taken of the children. Most of the children of whom no respiratory illness was reported belonged to three families. Yet the families wanted to

continue in the study when it was suggested that they should be released. Severe respiratory illnesses would certainly have been reported even in these families.

The attitude of people to this kind of long term study has been extensively described in the Cleveland study (23) and in the Virus Watch study (26). The same features were observed during this investigation. The readiness of the mothers to report respiratory illnesses varied and the reports of some mothers were invariably delayed. The idea of normal health seemed to be different and some mothers obviously accepted a child with a running nose as normal.

Comments on methods. In the family group the virus isolation specimens were sometimes taken several days after the onset of the respiratory illness and this, of course, reduced the chances of isolating the viruses responsible (7, 16). It was unexpectedly difficult to swab the pharynx in children aged 5-10 years without force and often properly taken samples were not obtained.

The tissue cultures were used in the laboratory in daily routine work. The adequacy of the methods used for isolation of adenoviruses was shown by Mäntylä (44) and for isolation of RS virus by Berglund (1). In the fall of 1965, U-cells and during several periods HeLa cells showed spontaneous degeneration and detachment of cells. Because of this, the adequacy was not maintained all the time. The sensitivity of primary monkey kidney cells is considered to be sufficient for recovery of myxoviruses (12). During this investigation the growth of these cells was often poor and spontaneous detachment of

from 18 infants, while bacterial tonsillitis and otitis media without respiratory symptoms were observed in 3 infants.

In the children aged 2—6 years 29 episodes of communicable diseases of childhood were reported 13 measles, 9 varicella 5 rubella and 2 cases of mumps. Diarrhea occurred in 10 children

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of infants in the family group could have been 3 times as high as that observed during the present study. The commonly reported inverse relation of respiratory illness rate and age was also observed in this study (26).

The patterns of acute respiratory illnesses in the infants of the nursery and family groups showed a somewhat similar seasonal variation. The pattern of acute respiratory illnesses in the family group did not resemble the pattern generally observed elsewhere in other geographic regions for the acute respiratory illnesses of children, with high fall and winter peaks (23, 26). In this study there was a decrease in the occurrence of acute respiratory illnesses in midwinter. This may be correlated with the climate in Finland. In midwinter a very cold frost period (from -1 to -20°C) sometimes continues for months without a break. This has restricted the contacts of the infants in the family group to a minimum. During this study the frost period was particularly cold and long during the winter of 1965-1966.

Etiologic results. The ratio of the acute respiratory illnesses with specific virus etiology to the total number of illnesses (approximately 40 per cent) was of the same order as in several other studies of acute respiratory infections in children (1, 14, 17, 33). Only in the infants of the nursery was the total positive rate lower (31 per cent).

RS virus was observed as an etiologic agent in 11 to 14 per cent of the respiratory illnesses among the infants and children of the family group and in 7 per cent of the illnesses in the infants of the nursery group. The infection rate observed in the family group was higher than that reported by Chanock and Parrott (17) but lower than in the series of Hilleman (33) and in the WHO survey of serologic studies of hospitalized patients (14). Parainfluenza viruses were observed in 7 to 11 per cent, the same rate as reported by Chanock and Parrott (17). In the infants of the nursery group the rate was low. In the family group parainfluenza

virus types 1^a and 3 occurred in the ratio usually observed. Influenza A infections occurred only in one-tenth of the families, representing 2 to 7 per cent of the respiratory illnesses of the infants and children of the family group.

Acute respiratory illnesses associated with infections of adenovirus types 1-7 were observed in this long-term study in a rate hitherto only reported to occur during adenovirus epidemics. In this series, in the infants of the nursery group an adenovirus infection, proved by a significant CF or HI antibody increase and in 41 per cent of these also by an isolation, was detected in 18.6 per cent of the acute respiratory illnesses. Adenovirus type 5 was prevalent, and infections with types 1 and 6 were also frequent. In some cases, adenovirus infections were observed concurrently with RS virus infections, and 14 isolations of adenoviruses, of which one-third were sporadic, were not followed by an antibody increase.

In the infants of the family group adenoviruses were associated with 12.5 per cent of the acute respiratory illnesses. Double infections with RS and parainfluenza virus infections were observed and in addition, 6 adenoviruses not followed by a significant antibody rise were isolated. In children aged 2-6 years 17 per cent of the respiratory illnesses were associated with adenoviruses. In the family group types 1 and 6 were the commonest in infants, and types 7 and 1 in children aged 2-6 years. In the older family children infections due to type 3 were frequently observed.

In the series of Laxdal *et al.* (4) the overall infection rate with adenoviruses in hospitalized patients was 11.6 per cent. Moffet *et al.* (49) isolated adenoviruses in 6 per cent from infants with no symptoms of illness, but in most of these cases the viruses were recovered only from anal washings. In Sutton's study the recoveries of adenovirus types 1, 2, and 5 were found to be independent of any illness in the children. The nine infants, whose sera

cells a few days after inoculation frequently occurred. In addition the direct inoculation technique with the rectal swabs often caused toxic degeneration in the cells.

Berglund has shown that the diagnostic efficiency of the OF test is 86 per cent in RS virus infections of children (7). In para-influenza virus infections, a heterotypic antibody response is known to occur in CF and HI tests. In children particularly with para-influenza virus type 1 infection a heterotypic rise to type 3 often occurs (16-19). In this study several concurrent rises to para-influenza virus types 1 and 3 were observed and if no virus was isolated the type of the parainfluenza virus infection remained undetermined.

In the studies of Vargosko *et al.* (71) only 19 per cent of all the infants and children from whom adenoviruses had been isolated developed an antibody rise in the OF test, yet the ratio was 39 per cent in those who had a respiratory illness and from whom adenovirus types 1, 2, 3, 5 and 7 were isolated. Similarly in the studies of Schmidt *et al.* (60) 32 per cent of infants and young children with adenovirus type 1, 2, 3 and 5 isolations had a significant increase in homotypic neutralizing antibody, 23 per cent in OF antibody and 20 per cent in HI antibody on kaolin treated sera. In HI tests very few heterotypic antibody increases were seen in children. The sensitivity of CF test in adenovirus infections was also evaluated by Iortnov (54). In 39 per cent of the infants and children with lower respiratory disease, from whom adenovirus infections were detected by isolation and significant increase in homologous neutralizing antibody no corresponding increase in OF antibody occurred. In the present study neutralizing antibodies to adenoviruses were not tested and the occurrence of adenovirus infections was based only on the results of CF and HI tests, thus the importance of adenovirus may have been underestimated.

The computer was of invaluable aid in the

analysis of the data because of the great number of different data recorded. Especially the possibility to list selected data quickly made it possible to study various aspects. In addition the dependence of the data on a great number of dates made the use of a computer necessary.

Occurrence of acute respiratory illness. The rates of the acute respiratory illnesses observed in this study 6.3 per person year in the infants of the nursery group, 2.5 per person year in the infants of the family group and an even smaller number in the other children and parents, differed greatly from the rates found in some other studies. In the Cleveland study (23) a mean respiratory illness rate of 7 to 8 per person year was observed in the infants. In Junior Village the total illness rate was 11 per person year (5). Sutton reported a rate of 8 respiratory illnesses per person year in a nursery (68). In the Virus Watch study a respiratory illness rate of 6 per person year was observed in children aged 0-5 years (26). The studies in the Edinburgh nursery revealed 5.2 respiratory illnesses per person year and the studies in the children's home in Kansas City 2.7 respiratory illnesses per person year (63). Backstrom-Jarvinen *et al.* have studied the pattern of illnesses from birth to 5 years of 88 'model children' living in Helsinki, Finland. During the first year of life an incidence of 2.3 febrile respiratory illnesses was observed, during the second year 1.2, in the 3rd year 1.0, in the 4th year 0.6 and in the 5th year 0.5 per person year (3). In the same nursery now studied Berglund *et al.* (8) earlier observed a rate of 4.8 respiratory illnesses per person year. The rate observed in the present study is somewhat higher which might be due to the special emphasis on the occurrence of acute respiratory illnesses during this study. The rate of acute respiratory illnesses in the family group was probably too low because short episodes may not all have been reported, but it seems unlikely that the rate of respiratory illnesses

of infants in the family group could have been 3 times as high as that observed during the present study. The commonly reported inverse relation of respiratory illness rate and age was also observed in this study (26).

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were tested already had Cf antibodies and neutralizing antibodies to the types of adenoviruses recovered. In the present study the adenovirus isolations not followed by a significant antibody rise were not included in the etiologic group and their significance remained obscure.

Clinical features. Among the infants of the nursery group lower respiratory tract infections (LRI) were observed more often in the illnesses associated with detected virus etiology than in the illnesses with unknown etiology. This was due to RS and parainfluenza virus infections. In both groups of infants, adenovirus infections were mainly associated with upper respiratory tract illnesses (URI). In illnesses of unknown etiology IRI was diagnosed more often in the infants of the family group than in the infants of the nursery group. This may possibly indicate inadequacy of the sampling procedure in the infants of the family group.

The illnesses with detected virus etiology were more often febrile than the illnesses of unknown etiology. This was due to RS and parainfluenza virus infections in the infants of the nursery group but in the infants of the family group most of the adenovirus infections were likewise febrile. This might be associated with the fact that the occurrence of adenovirus types varied in these groups but also with the difference in the ages. On the other hand febrile illnesses were certainly more readily reported in the family group than minor illnesses without fever. Of the illnesses with unknown etiology more were febrile in the infants of the family group than in those of the nursery group and this also suggests that the illnesses were due to the agents studied even though the virologic identification was missed.

Similarly the survey of the signs and symptoms emphasized the importance of the agents studied. Otitis media was more common in the illnesses with detected virus etiology than in the illnesses of unknown etiology among the infants of the nursery group. In

the infants of the family group otitis media was often found in RS and parainfluenza virus infections. Cough, laryngeal symptoms and cervical lymphadenopathy were observed more often and rhonchi less often in the illnesses with detected virus etiology. In the illnesses with unknown etiology rhonchi and otitis media were observed more often in the infants of the family group than in those of the nursery group.

The duration of all acute respiratory illnesses was longer in the infants of the nursery group than in those of the family group.

Outbreaks of virus infections. RS virus infections occurred in outbreaks, in the family group during both fall periods but in the nursery as a single outbreak, when all the infants contracted the infection. In addition a single outbreak of parainfluenza virus infection due to type 3 was observed in the nursery at a time when this infection was prevalent in the infants and children of the families studied. Once in both infant groups the occurrence of illnesses associated with adenoviruses was observed at the same time. The outbreaks of adenovirus types 2, 8 and 7 in the nursery were not correspondingly observed in the family group. Outbreaks due to other parainfluenza viruses, influenza A2, and Coxsackie B type 2 in the family group were not noticed in the infants of the nursery group.

In conclusion it can be pointed out that the infants in the nursery studied represented a group with a high respiratory illness rate characterized by frequent adenovirus infections. Only occasionally did the viruses causing acute respiratory illness in the family children invade the nursery at the same time. Accordingly such isolated nurseries are not representative index populations for the acute respiratory illnesses in the surrounding community. By a surveillance of even a small group of families more virus infections can be detected and such a group probably more nearly reflects the epidemiologic pattern of acute viral respiratory infections in a community.

Summary

The significance of respiratory syncytial (RS) parainfluenza, influenza and adenoviruses in the etiology of acute respiratory disease in children was evaluated and the value of a group of institutionalized children as an index of the respiratory disease among children in the surrounding community was studied by a long term survey. The population in the two study groups consisted of families including at least one infant and of infants residing in a nursery in the same city. The mean number of infants in the nursery was 15 and in the families 40.

All acute respiratory illnesses occurring during the year surveillance were studied by virus isolation, serologic tests and clinical examination. The total observation time for infants in the nursery group was 34 person-months and 1031 person-months for the infants in the family group. The total person-months observed in the family group were 4577.

A total of 528 acute respiratory illnesses were studied and virus etiology was established in 40 per cent of the 410 illnesses in the family group and in 31 per cent of the 188 illnesses in the nursery group.

In the infants of the nursery group the rate of respiratory illnesses was 5.3 per person-year. In the infants of the family group the illness rate 5 per person ear was only about one third of the rate in the nursery. The mean prevalence of respiratory symptoms was 33 per cent in the infants of the nursery group and 10 per cent in the infants of the family group. On average at any one time infants in the nursery and 4 infants in the family group had respiratory illness symptoms.

The highest incidence of acute respiratory

illnesses occurred in the fall and the spring and an unexpectedly low incidence was observed in the family group during the frost period in midwinter.

In the infants of the nursery group, 1 per cent of the illnesses were associated with RS virus, 4 per cent with parainfluenza virus type 3 and 19 per cent with adenoviruses, mainly with types 5 and 2. In the infants of the family group, 1* per cent of the illnesses were associated with RS virus, 11 per cent with parainfluenza, * per cent with influenza A2, and 12 per cent with adenoviruses.

The clinical observations further emphasized the importance of these viruses in the respiratory disease of children. Among the infants of the nursery RS virus and parainfluenza viruses were found to cause involvement of the lower respiratory tract (LRI) more often than the unknown etiologic agents. The illnesses with detected virus etiology were more often febrile than the illnesses of unknown etiology. Otitis media was observed more often in illnesses with detected virus etiology in the infants of the nursery group. This was due to RS virus infections. In the infants of the family group otitis media occurred in RS and parainfluenza virus infections, but also in illnesses with unknown etiology.

In the outbreaks of acute respiratory illness identical etiology was seen only once, when the parainfluenza virus type 3 was simultaneously prevalent as a sudden outbreak in both groups. Two RS virus outbreaks occurred in the families in both fall seasons, but only one RS outbreak occurred in the nursery. In the nursery outbreaks of adenovirus types 4, 5 and 7 occurred and corre-

sponding outbreaks were not seen in the families. The outbreaks of parainfluenza virus types 1, 2, influenza A2 and Coxsackie B type 2 were not noticed to occur in the nursery and adenovirus type 3 did not occur. In both groups, in a third of the outbreaks the etiology remained totally unknown.

The conclusion is drawn that the infants in the nursery studied were a group with a high respiratory illness rate and frequent adenovirus infections due to different adeno-

virus types than those observed in the families. The viruses causing acute respiratory illnesses in the children of families in the surroundings only occasionally invaded the nursery at the same time. Thus such isolated groups of institutionalized children as the infants in the nursery studied are not representative index populations for respiratory disease in the children of the community as a whole.

Acknowledgments

I am deeply grateful to Professor Pekka Halonen, M.D. Head of the Department of Virology for the continuous support he has given me during this study. It was he who introduced me to virology and his extensive knowledge and experience in the field of respiratory viruses have been of invaluable help to me. He has placed the resources of his laboratory at my disposal and permitted his staff to assist me. In the preparation of the manuscript his criticism has been of great help.

I am grateful to Professor Tuomas Peltonen, M.D. Head of the Children's Hospital, University of Turku, my teacher in pediatrics, for his encouragement. He and Professor Halonen together suggested this subject to me. Professor Peltonen allowed me to use the facilities of the outpatient clinic in his hospital for collection of specimens.

I am greatly indebted to Professor Johan W. Kärholm, M.D. Head of the Hospital for Infectious Diseases in Turku. As an assistant physician in his hospital I first had an opportunity to participate in research work concerning the respiratory infections of children. As physician-in-charge he allowed me to collect specimens from the Nursery.

I record my indebtedness to the late Associate Professor Jari Axel Grönroos, M.D. Department of Medical Microbiology University of Turku, for co-operation, friendship and interest for my work.

I am grateful to Associate Professor Kanko-Kuivalainen, M.D. Children's Hospital, University of Turku, for his criticism of the manuscript.

I wish to express my gratitude to my colleagues at the Department of Virology for

their help and interest during my work. I am much obliged to Dr. Rauno Mäntyjärvi, M.D. for his advice on problems of virology and his criticism of the manuscript and to Dr. Bo Berglund, M.D. for co-operation and advice based on his extensive knowledge of respiratory syncytial virus.

I wish to thank the personnel of the Department of Virology, the Outpatient Clinic of the Children's Hospital, and the Nursery and the health sisters at the Child Welfare Centers for their assistance and courtesy. In particular I am grateful to Mrs. Leena Nurmi for technical assistance during the whole study. Mrs. Maija Aro and Mrs. Sirkka-Liisa Koskinen for their secretarial assistance.

My sincere thanks are due to the families which participated in this study.

I am grateful to Mr. Pekka Aho, M.Sc., Institute of Applied Mathematics, University of Turku, for programming the data processing. Mrs. Aili Ryyänen, M.A., and her assistant at the Library of the Medical Faculty University of Turku, for their help in collecting the literature, and Mrs. Jean Margaret Perttunen, B.Sc., for revising the language of the manuscript.

This study was personally supported by the National Research Council for Medical Sciences. Grants from the Finnish Federation of University Women and the Foundation for Paediatric Research in Finland are gratefully acknowledged. The technical side of the work has been supported by grants to the institution from the Sigrid Jusélius Foundation.

Turku, February 1969

Leena Viikari

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The conclusion is drawn that the infants in the nursery studied were a group with a high respiratory illness rate and frequent adenovirus infections due to different adeno-

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Acknowledgments

am deeply grateful to Professor Pekka Hälönen, M.D. Head of the Department of Virology for the continuous support he has given me during this study. It was he who introduced me to virology and his extensive knowledge and experience in the field of respiratory viruses have been of invaluable help to me. He has placed the resources of his laboratory at my disposal and permitted his staff to assist me. In the preparation of the manuscript his criticism has been of great help.

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I am grateful to Associate Professor Kauko Korhonen, M.D. Children's Hospital, University of Turku, for his criticism of the manuscript.

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their help and interest during my work. I am much obliged to Dr. Ilmari Mäntylä, M.D., for his advice on problems of virology and his criticism of the manuscript and to Dr. Bo Berglund, M.D. for co-operation and advice based on his extensive knowledge of respiratory syncytial virus.

I wish to thank the personnel of the Department of Virology, the Outpatient Clinic of the Children's Hospital, and the Nursery and the health sisters at the Child Welfare Centers for their assistance and courtesy. In particular I am grateful to Mrs. Leena Hursti for technical assistance during the whole study. Mrs. Maija Aro and Mrs. Sirkka-Liisa Koskinen for their secretarial assistance.

My sincere thanks are due to the families which participated in this study.

I am grateful to Mr. Pekka Aho, M.Sc., Institute of Applied Mathematics, University of Turku, for programming the data processing, Mrs. Aili Ryyänen, M.A. and her assistant at the Library of the Medical Faculty University of Turku, for their help in collecting the literature, and Mrs. Jean Margaret Perttunen, B.Sc., for revising the language of the manuscript.

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CARDIOVASCULAR RESPONSE OF THE
NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA
AND METABOLIC ACIDOSIS

BY ANTTI KOIVIKKO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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ACTA
PÆDIATRICA
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SUPPLEMENT 191 1969

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AND METABOLIC ACIDOSIS

BY ANTTI KOIVIKKO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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*From the Cardiorespiratory Research Unit the Department of Physiology
and the Children's Hospital of the University of Turku, Turku, Finland*

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KIRJAPAINO POLYTYPOS TIEKKI 1969

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Printed in Finland

KIMJAPAINO POLYTYPOS TURKU 1909

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Symbols and abbreviations

CO	cardiac output	_____
HR	heart rate	○ — — — — — ○
SV	stroke volume	+ — — — — — +
CBV	central blood volume	□ — — — — — □
SV/CBV	ratio of SV to CBV	_____
AT	appearance time	— ~ ~ ~ ~ ~ x

Introduction

Fetal and newborn mammals tolerate longer periods of asphyxia than adults. This is very appropriate because disorders of oxygen transport from the placenta or lungs to the peripheral tissues develop very easily in fetuses and newborn infants. The reasons for the good asphyxia tolerance of the latter are probably special adjustments of the cellular energy metabolism and the cardiovascular function.

The cardiorespiratory system of a newborn reacts similarly to some stimuli as that of an adult. Important differences exist, however. The pulmonary vascular resistance remains at higher level in newborn infants than in adults for several postnatal weeks, the fetal shunt opens easily in response to hypoxia during the first days after birth and the acid base values of infants during the first week differ somewhat from the values in adults. The arterial response to arterial hypoxia is weaker in newborn infants than in adults, and during hypoxia the pulmonary vascular resistance increases comparatively more than later in life. These characteristics of fetal and neonatal mammals, although appropriate before birth, do not always appear so after birth.

In adult mammals the circulation will preferentially supply oxygen to the most important organs during shock and severe as-

phyxia. This aspect has been little studied in neonatal mammals, but there is evidence that a similar adjustment of the circulation may occur in newborn and also fetal mammals.

The myocardial and brain tissues of newborn mammals may function for some time with only anaerobic energy metabolism. This ability is not without limit and therefore physicians have to support the most important functions. The most successful methods of treatment are positive-pressure ventilation with oxygen and infusion of alkaline buffers and glucose. Many other methods have been suggested, but in general they have not been successful.

Treatment with oxygen and alkali-glucose infusion are known to improve the prognosis of asphyxiated infants, but little is known about the physiological basis of these therapeutic methods. From a clinical standpoint, it is important to know the course of hemodynamics during asphyxia. Furthermore, it would be of value to know the separate effects of hypoxia, hypercapnia and metabolic acidosis. Thus it seemed that these aspects would be worth experimental study. A preliminary report of some of the results of hypoxia and hypercapnia experiments with newborn lambs has already been published (72).

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Symbols and abbreviations

CO	cardiac output	_____
HR	heart rate	○ — — — — — ○
SV	stroke volume	+ _____
CBV	central blood volume	□ — — — — — □
SV/CBV	ratio of SV to CBV	_____
AT	appearance time	x — — — — — x

TABLE 1 Flow rates in different parts of the circulation of infants, lambs and calves in different stages of development. All values are given in ml/min kg if not otherwise mentioned.

	Umbilical flow	RV output	LA output	Cardiac output	Method	Ref
Human fetuses 10-28 gest. weeks	100-130			540 ml/min 2.5 l/min m ²	Electromagnetic flowmeter	(7)
Newborn infants					Dye dilution	(83)
Newborn infants — early clamped — late clamped		2.11 l/min m ² 103	2.67 l/min m ² 307		Dye dilution	(4)
Newborn premature infants — highest RD — 1th RD				8.53 l/min m ² 4.5	Dye dilution	(128)
Infants — 1 year — 3 year				163 131	Estimated	(111)
Fetal lambs — 00-90 gest. day — 1 term	120-250 124±31	Lamblased			Venous occlusion plethysmogr	(24)
Fetal lambs — 60 gest. day — 1 term	100 120				Venous occlusion plethysmogr and flowmeter	(1)
Fetal lambs — 91 gest. days — at ewe					Cardiometer	(12)
Newborn lambs					Fick	(25)
Fetal lambs at term					Dye dilution	(84)
Newborn lambs — 1 fore catheter — 1st catheter					Electromagnetic flowmeter	(8)
Newborn lambs					Fick	(98)
Newborn lambs					Dye dilution	(117)
Newborn lambs — neonatal — at 4 wks						(101)
		179.7±56.4	181.7±50.6			
		129	97			
		189	164			
				225±20		
				4.3		
				190		
				140		

From data on blood volume and circulation time.

appearance and if the central blood volume per kilogram remained unchanged, but the variation of central blood volume with age is not known.

The circulation time in newborn infant seems to be only slightly affected by the activity of the infant. In adults, the circulation time tends to decrease somewhat during physical exercise (86). The above data that the circulation time does not vary significantly with the rate of injection (arterial or central vein) (66, 116) supports the view that the circulation time is less dependent on the distance

than on the blood volume and flow rate between two sites.

According to Hamilton *et al.* (56) the central blood volume (CBV) is the volume of blood between the venous injection and arterial registration sites. This volume cannot be accurately defined physiologically or anatomically. Hegghia *et al.* (60) reported that it amounts to 38±6 per cent of the total blood volume in normal adult. This CBV has not been studied in infants or children.

A linear relationship has been found between the

Previous Investigations

BASAL CIRCULATORY VALUES IN THE FETAL AND NEONATAL PERIODS

Table I presents previously reported flow rates in different parts of the fetal and neonatal circulation. Small et al (7) recorded umbilical blood flows of 100 to 130 ml/min kg in human fetuses. There was no variation in the flow rate with increasing gestational age from 10 to 28 weeks. If the umbilical blood flow in human fetuses were 65 per cent of the total cardiac output (20) the latter would be about 150 to 200 ml/min kg.

Irons and Cunnick (28) were the first to use the dye dilution method in a study of the circulation in newborn infants. They obtained a cardiac index of 2.5 l/min/m^2 . They also reported that the cardiac output was higher in infants over 15 hours old than in younger infants. Recently Arellano et al (4) measured the output of each ventricle in newborn infants and obtained high values for the left ventricular output than Irons and Cunnick. The left ventricular output exceeded the right ventricular output. The outputs were higher in infants in which the umbilical cord was clamped early than in infants in which the cord was clamped late. The lower cardiac output in the former group was probably a compensatory phenomenon resulting from polycythemia arising from the low ring of the pulmonary valve which occurs within a few hours after birth in late-clamped infants (29). The cardiac output per square meter of body area in newborn infants seems to be low to the lower normal limits in adults, which is taken to be about 2.0 l/min/m^2 (30).

Using a cannulated Blalock et al (13) measured combined left and right ventricular outputs of 707 $\pm 210 \text{ ml/min/kg}$ in fetal lambs on the 66th gestational day and at term respectively. These results agree well with later observations. Millen blood flow (14) who in lambs found that 65 per cent of the total fetal cardiac output flows to the placenta (23). Electromagnetic measurement of aortic and pulmonary arterial blood flow by Small et al (9) also agrees with the total cardiac output which agrees with the result of Blalock et al.

However much larger cardiac outputs were measured by Malhotra et al (31) using the dye dilution method.

The output of the ventricles of the lamb barely increases when respiration begins, but the output of the left ventricle increases more than that of the right ventricle (9). This difference arises immediately after the lungs are inflated (9). The measured cardiac outputs of neonatal lambs are divergent. Applying the direct Fick principle Cross et al (32) measured a value of 3.5 l/min/kg , whereas Blalock et al (17) obtained the much higher value 4.5 l/min/kg using the dye dilution method.

The measurement of circulation time has been used as a hemodynamic tool in assessing hemodynamic changes, but the time does not alone give sufficient information on the state of the circulation. The recently used dye dilution method gives much additional information.

Circulation times over different distances obtained by different methods are shown in Table II. It will be noted that methods (biplanimetry and fluorocine) based on visual observation usually give longer circulation times than the dye dilution method, in which the subjective error is small.

The circulation time from aorta to femoral artery junction or carotid artery to the aorta varies markedly in the newborn infant (33). This time decreases to about four seconds in the first three weeks after birth (34). The decrease of the appearance time was observed also by Lowrey et al (77). After the initial decrease the appearance time increases with increasing age and body size to a value of 9 to 10 seconds in a adult (35).

The high gas circulation time from birth to adulthood is small in comparison with the increase in blood size. The circulation time from aorta to iliac femoral artery related to the ratio of the arterial blood volume to the cardiac output. The cardiac output calculated from the multi-film technique (34) is about 170 ml/min/kg in newborn infants, whereas according to Millen et al (14) the cardiac output is about 80 ml/min/kg in a adult. This decreased cardiac output would explain the long

Table I. Flow rates in different parts of the circulation of infants, lambs and calves in different stages of development. All values are given in ml/min kg if not otherwise mentioned.

	Umbilical flow	RV output	LV output	Cardiac output	Method	Ref.
Human fetuses 10-25 gest. wks	100-120			540 ml/min 2.5 l/min m ²	Electromagnetic flow meter	(7)
Newborn infants					Dye dilution	(95)
Newborn infants — early clamped — lat clamped		11 l/min m ² 100	3.67 l/min m ² 3.67		Dye dilution	(4)
Newborn premature infant — 10h RD — 14h RD				5.53 l/min m ² 4.63	Dye dilution	(129)
Infants — 1 year — 2 year				163 131	Estimated	(131)
Fetal lambs — 60-90 gest days — at term	180-250 138±31				Venous occl. plethysmogr.	(4)
Fetal lamb — 80 gest day — at term	180 130				Venous occl. plethysmogr and flowmeter	(1)
Fetal lamb — 93 gest days — at term		Combined			Cardiometer	(12)
		365				
		240				
Newborn lambs		230			Fick	(28)
Fetal lambs at term		179.7±36.4	181.7±30.6		Dye dilution	(84)
Newborn lambs — before castration — after castration		138 169	97 164		Electromagnetic flow meter	(9)
Newborn lambs				285±20	Fick	(26)
Neonatal lambs (1 hr) — neonatal — 18 wks				433 190 140	Dye dilution	(117) (101)

From data on blood volume and circulation time.

preparation time of the central blood volume per kilogram remained unchanged, but the variation of central blood volume with age is not known.

The circulation time in newborn infant seems to be only slightly affected by the activity of the infant (11). In adults, the circulation time tends to decrease somewhat during physical exercise (96). The observation that the circulation time does not vary significantly with the site of injection (arms or central veins) (66, 116) supports the view that the circulation time is less dependent on the distance

than on the blood volume and flow rate between the sites.

According to Hamilton *et al.* (36) the central blood volume (CBV) is the volume of blood between the venous injection and arterial registration sites. This volume cannot be accurately defined physiologically or anatomically. Hegglin *et al.* (90) reported that it amounts to 38±6 per cent of the total blood volume in normal adult. This CBV has not been studied in infants or children.

A linear relationship has been found between the

Previous Investigations

BASAL CIRCULATORY VALUES IN THE FETAL AND NEONATAL PERIODS

Table I presents previously reported flow rates in different parts of the fetal and neonatal circulation. Asanali *et al.* (7) recorded umbilical blood flows of 100 to 130 ml/min kg in human fetuses. There was no variation in the flow rate with increasing gestational age from 10 to 28 weeks. If the umbilical blood flow in human fetuses were 65 per cent of the total cardiac output (29) the latter would be about 160 to 200 ml/min kg.

Free and Cassels (98) were the first to use the dye dilution method in a study of the circulation in newborn infants. They obtained a cardiac index of 2.5 l/min m². They also reported that the cardiac output was higher in infants over 15 hours old than in younger infants. Recently Arellano *et al.* (4) measured the output of each ventricle in newborn infants and obtained higher values for the left ventricular output than Free and Cassels. The left ventricular output exceeded the right ventricular output. The outputs were higher in infants in which the umbilical cord was clamped early than in infants in which the cord was clamped late. The lower cardiac output in the former group was probably a compensatory phenomenon resulting from polycythemia arising from the lowering of the plasma volume which occurs within a few hours after birth in late-clamped infants (126). The cardiac output per square meter of body area in newborn infant seems to be close to the lower normal limit in adults, which is taken to be about 2.6 l/min m² (60).

Using a cardiometer Barcroft *et al.* (1) measured combined left and right ventricular outputs of 39 and 40 ml/min kg in fetal lambs on the 95th gestational day and at term, respectively. These results agree well with later observations on umbilical blood flow (14) when it is borne in mind that 65 per cent of the total fetal cardiac output flows to the placenta (29). Electromagnetic measurements of aortic and pulmonary arterial blood flow by Asanali *et al.* (9) also gave values of the total cardiac output which agree with the results of Barcroft *et al.*

However, much larger cardiac output were measured by Mahon *et al.* (84) using the dye dilution method.

The outputs of the ventricles of the lamb clearly increase when respiration begins, but the output of the left ventricle increases more than that of the right ventricle (9). This difference arises immediately after the lungs are inflated (9). The measured cardiac outputs of neonatal lambs are divergent. Applying the direct Fick principle Cross *et al.* (96) measured a value of 325 ml/min kg, whereas Stahlman *et al.* (117) obtained the much higher value 445 ml/min kg using the dye dilution method.

The measurement of circulation time has been used as a diagnostic tool in diseases involving hemodynamic changes, but the time does not alone give sufficient information on the state of the circulation. The recently used dye dilution method gives much additional information.

Circulation times over different distances obtained by different methods are shown in Table II. It will be noted that methods (histamine-rash and fluorescein) based on local observation usually give longer circulation times than the dye dilution method, in which the subjective error is small.

The circulation time from arm to face (lip junction or ear) seems to be about seven seconds in the newborn infant (66). This time decreases to about four seconds during first three weeks after birth (66). This decrease of the appearance time was observed also by Loefer *et al.* (77). After the initial decrease, the appearance time increases with increasing age and body size to a value of 9 to 10 seconds in an adult (60).

The change in circulation time from birth to adulthood is small in comparison with the increase in body size. The circulation time from arm to lip, for example, is related to the ratio of the central blood volume to the cardiac output. The cardiac output calculated from the results of Free and Cassels (98) is about 170 ml/min kg in newborn infants, whereas according to Heggin *et al.* (60) the cardiac output is about 40 ml/min kg in an adult. The decreased cardiac output could explain the longer

begins this review with description of the dull circulation during hypoxia.

In the following the term hypoxia refers to arterial hypoxia unless otherwise stated. The term asphyxia refers to all states including hypoxia, hypercapnia and/or metabolic acidosis that result from reduced gas exchange.

Hemodynamic changes

The high-output pattern

Local arteriole arterial hypoxia induces an increased blood flow by dilating the arterioles in most organs (31). This counteracts the effect of decrease in the oxygen carrying capacity of the blood. It seems that oxygen deficiency is the regulating factor because maximal control and increased levels of carbon dioxide, lactic acid and other agents known to cause arteriole dilation are not necessary for vasodilatation in hypoxia (34). Every vascular bed is, however, under constant neurohumoral control which may counteract the direct effect of hypoxia. This system is assumed to work via modulating β - and γ -receptors and vasoconstricting receptors in arterioles. Dermal and renal arterioles do not dilate during hypoxia; this suggests dominant neuronal vasoconstriction. Most of the renal vessels do not exhibit reactive hyperoxia, which is seen in the renal vessels in other tissues, mainly muscle hypoxia induces pronounced vasodilatation. In cerebral and coronary vascular beds, the lowered partial oxygen pressure is superimposed on other factors having an influence on the state of the arterioles (34).

In most studies here the direct effect principle has been applied to measure the cardiac output in normal animals (41, 43, 45, 118, 123) in dogs (2, 44, 74, 78, 119) and in sheep (38). Increased cardiac output has been observed to result from hypoxia. A consistent increase in blood flow has been found during hypoxia when the dye dilution has been used to estimate the cardiac output in man (36, 41, 44, 45, 107, 120, 123) and rat (178).

In man, increased cardiac output results from an increase in both the stroke volume and the heart rate in normal man. The stroke volume increases relatively more than the heart rate (39, 41). The heart rate has been stated to increase during hypoxia in the dog but the stroke volume only slightly (69, 120). In contrast, Harrison and Blacklock (59) observed only slight increase in the heart rate and large increase in the stroke volume in dogs.

The mean arterial pressure rises only slightly in man during hypoxia (39, 123). This reflects the

effect of the peripheral vasodilatation. Some variation in the mean arterial pressure is seen in hypoxia in the dog (3, 40).

The central blood volume does not change during hypoxia in man (39, 43). Measurements of central blood volume in anesthetized dogs has shown that an increase occurs (11, 61, 81, 107, 120). A large increase occurs also in the pulmonary blood volume in unanesthetized dogs during hypoxia (68).

All reports seen by the author suggest that the circulation time decreases during hypoxia. Both the arm-to-ear and lung-to-ear appearance times decrease clearly during hypoxia in normal adults (13). A decrease in the aortic transit time has been measured by the dye dilution method in man (from 12.5 to 10.7 sec.) (45) and in unanesthetized dogs (from 7.8 to 6.1 sec.) (68) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during \bar{Dn} , i.e. under severe asphyctic conditions, and in rabbits in severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions of the circulation are practically closed (40, 109). The renal blood flow almost stops in the seal, as the blood flows through the abdominal aorta, kidney and mesenteric arteries are greatly reduced in the dog during submersion (40). The carotid arterial blood flow of the diving seal decreases considerably but remains higher than any other peripheral flow rate (40). In the submerged greyhound the coronary blood flow remains unchanged (40). Bradycardia during \bar{Dn} can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturate anesthesia (40).

The completeness of the peripheral vasoconstriction during \bar{Dn} is apparent from the observation that the lactic acid concentration of the peripheral blood increases only little during the \bar{Dn} but increases immediately after surfacing when the peripheral circulation is opened again (109). In addition to the cardiovascular changes that must occur reduction of the metabolic rate becomes the extreme oxygen uptake of seals and other diving animals after the submersion period does not correspond to the calculated basal oxygen requirement during the submersion period (109). The basic reason for this lowered oxygen consumption is not known.

Although the high output pattern may result if rabbits are made moderately hypoxic, low output pattern is like the cardiac output decreases abruptly for few minutes occurs during severe hypoxia in

TABLE II Indicator appearance times (in seconds) over different distances in mammals as determined by different methods.

	Hand to face lip or ear	Umbil. vein to lip or ear	Pulmonary transit time	Method	Ref
Human beings					
1st day	7.0			Dye dilution	(66)
3rd week	4.3				
< 5 days	10.0			Fluorescein	(77)
1-4 days	7.8			Fluorescein	(83)
4-12 months	10.0				
< 1 year	14.8			Histamine rash	(111)
< years	7.0			Fluorescein	(136)
3-13 years	11.5				
< years	6.5			Fluorescein	(46)
adult	9-10			Dye dilution	(60)
newborn		4.8		Fluorescein	(116)
1st day		3.0		Dye dilution	(98)
newborn			1.83	Dye dilution	(14)
Newborn lambs					
— before ventil.			9-17	X-ray contrast	(5)
— after ventil.			1.0-1.7		
Newborn dogs			1.0	X-ray contrast	(50)
Newborn pigs			0.8-1.3		(53)

stroke volume and the CBV (50). This relationship is maintained when the position is changed and during anesthesia (48). Heggin *et al.* (60) give a value of 0.048 ± 0.005 for the ratio of stroke volume to CBV in a normal adult.

CARDIOVASCULAR ADJUSTMENTS IN ACUTE ARTERIAL HYPOXIA

Oxygen seems to be the substance whose transport is most dependent on adequate peripheral blood flow. Guyton (54) states that the safety factor for oxygen transport is only threefold, whereas this factor is considerably larger for other nutrient wastes, 3-5-fold for carbon dioxide, 20-fold for fatty acids,

30-fold for glucose, 30-fold for amino acids, and 40-fold for nitrogenous wastes. It is also known that a decrease in cardiac output by one third causes hypoxia in most tissues, whereas a decrease of this magnitude does not reduce the overall transport of other substances. A decreased oxygen transport to mitochondria may result from a low ambient partial pressure of oxygen, insufficient gas exchange in the lungs, severe anemia, methemoglobinemia, carbon monoxide and cyanide poisoning, and physical effort. The cardiovascular adjustments seen to be roughly the same in arterial hypoxia and physical exertion (54).

Most of our knowledge of the circulatory changes during hypoxia is based on experimental data for adult mammals. The following are considered appropriate to

begin this review with description of the *dog* circulation during hypoxia.

In the following the term hypoxia refers to arterial hypoxia unless specified otherwise. The term *apnoea* refers to all states including hypoxia, hypercapnia and/or metabolic acidosis that result from a reduced gas exchange.

Hemodynamic changes

The high-output pattern

Local acute arterial hypoxia induces an increased blood flow by dilating the arterioles in most organs (33). This counteracts the effect of decrease in the oxygen-carrying capacity of the blood. It seems that oxygen deficiency is the regulating factor because arterial control and increased levels of carbon dioxide, lactic acid and other agents known to cause arteriolar dilatation do not seem necessary for vasodilation in hypoxia (34). In the awake rabbit, however, under constant arterial control which we counteract the direct effect of hypoxia. This system is maintained via modulating β -adrenoceptors and corresponding receptors in arterioles. Dermal and renal arterioles do not dilate during hypoxia; this suggests dominant arterial vasoconstrictor effect (31). Since animals do not exhibit reactive hyperaemia, which is seen in the renal vessels. In other tissues, mainly muscle hypoxia induces pronounced vasodilation. In renal and coronary vascular beds, the lowered partial oxygen pressure is superimposed on all other factors having an influence on the state of the arterioles (34).

In most studies, however, the direct Fick principle has been applied to measure the cardiac output in normal animals (41, 32, 81, 118, 120). In dogs (3, 44, 46, 79, 119) and in sheep (80) an increased cardiac output has been observed to result from hypoxia. A consistent increase in blood flow has been found during hypoxia when the dye dilution has been used to estimate the cardiac output in men (35, 47, 48, 107, 120, 123) and calves (78).

Increased cardiac output results from an increase in both the stroke volume and the heart rate in normal man. The stroke volume increases relatively more than the heart rate (33, 41). The heart rate has been found to increase during hypoxia in the dog, but the stroke volume only slightly (40, 120). In contrast Harrison and Blalock (34) observed only slight increase in the heart rate and large increase in the stroke volume in dogs.

The mean arterial pressure rises only slightly in man during hypoxia (38, 122). This reflects the

effect of the peripheral vasodilatation. Some variation in the mean arterial pressure is seen in hypoxia in the dog (3, 80).

The central blood volume does not change during hypoxia in man (39, 42). Measurements of central blood volume in anesthetized dogs have shown that an increase occurs (11, 61, 67, 107, 120). A large increase occurs also in the pulmonary blood volume in unanesthetized dogs during hypoxia (89).

All reports seen by the author suggest that the circulation time decreases during hypoxia. Both the arm-to-arm and lung-to-arm appearance times decrease clearly during hypoxia in normal adult (13). A decrease in the arm transit time has been measured by the dye dilution method in men (from 12.3 to 10.7 sec) (43) and in unanesthetized dogs (from 7.5 to 6.1 sec) (89) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during a dive or under severe asphyctic conditions, and is related to severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions of the circulation are practically closed (40, 103). The renal blood flow almost stops in the seal and the blood flows through the abdominal aorta, lumbar and vertebral arteries are greatly reduced in the dog during submersion (40). The carotid arterial blood flow of the diving seal decreases considerably but remains higher than any other peripheral flow rate (40). In the submerged greyhound the coronary blood flow remains unchanged (40). Bradycardia during diving can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturate anesthesia (40).

The completeness of the peripheral vasoconstriction during a dive is apparent from the observation that the lactic acid concentration of the peripheral blood increases only little during the dive but increases immediately after surfacing. Also the peripheral circulation is opened again (103). In addition to the cardiovascular changes there must occur reduction of the metabolic rate because the excess oxygen uptake of seals and other diving animals after the submersion period does not correspond to the calculated basal oxygen requirement during the submersion period (103). The basic reason for this lowered oxygen consumption is not known.

Although the high-output pattern may result if rabbits are made moderately hypoxic, low-output pattern in which the cardiac output decreases largely for a few minutes occurs during severe hypoxia in

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1—12 days	7.8			Fluorescein	(93)
2—15 months	10.0				
< 1 year	14.9			Histamine rash	(111)
< 2 years	7.0			Fluorescein	(136)
3—13 years	11.5				
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adult	9—10			Dye dilution	(60)
newborn		4.8		Fluorescein	(116)
1st day		5.8		Dye dilution	(68)
newborn			1.85	Dye dilution	(14)
Newborn lambs					
— before ventil.			2.9—4.7	X ray contrast	(5)
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stroke volume and the CBV (56). This relationship is maintained when the position is changed and during anesthesia (68). Heggin *et al.* (60) give a value of 0.048 ± 0.005 for the ratio of stroke volume to CBV in normal adult.

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Oxygen seems to be the substance whose transport is most dependent on adequate peripheral blood flow. Guyton (54) states that the safety factor for oxygen transport is only threefold, whereas this factor is considerably larger for other nutrients: wastes 23-fold for carbon dioxide 28-fold for fatty acids,

30-fold for glucose, 36-fold for amino acids, and 480-fold for nitrogenous wastes. It is also known that decrease in cardiac output by one third causes hypoxia in most tissues, whereas a decrease of this magnitude does not reduce the total transport of other substances. A decreased oxygen transport to mitochondria may result from a low ambient partial pressure of oxygen, insufficient gas exchange in the lungs, severe anemia, methemoglobinemia, carbon monoxide and cyanide poisoning, and physical effort. The cardiovascular adjustment seems to be roughly the same in arterial hypoxia and physical exercise (54).

Most of our knowledge of the regulatory mechanisms during hypoxia is based on peripheral data for adult mammals. Therefore it seemed appropriate to

gia this review with description of the adult circulation during hypoxia.

In the following the term hypoxia refers to arterial hypoxia unless mentioned otherwise. The term asphyxia refers to all states including hypoxia, hypercapnia and metabolic acidosis that result from reduced gas exchange.

Hemodynamic changes

The high-output pattern

Local and arterial hypoxia induces an increased blood flow by dilating the arterioles of most organs (33). This counteracts the effect of decrease in the oxygen-carrying capacity of the blood. It seems that oxygen deficiency is the regulating factor because neuronal control and increased levels of carbon dioxide, lactic acid and other agents known to cause arteriolar vasodilatation are not necessary for vasodilatation in hypoxia (34). Erythrocyte and is, however, under constant active humoral control which may counteract the direct effect of hypoxia. This system is assumed to work as modulating β and γ receptors and vasoconstricting receptors in arterioles. Renal and renal arterioles do not dilate during hypoxia; this suggests dominant neuronal vasoconstrictor effect (31). Since muscle do not exhibit reactive hyperemia, work as seen in the renal vessels. In other tissues, usually muscle, hypoxia induces pronounced vasodilatation in cerebral and coronary vascular beds, but lowered partial oxygen pressure is superimposed on all other factors having an influence on the state of arterioles (34).

In most studies here the direct Fick principle has been applied to measure the cardiac output in normal humans (11, 23, 32, 118, 120) in dogs (3, 4, 24, 36, 119) and in sheep (26) an increased cardiac output has been observed to result from hypoxia. A consistent increase in blood flow has been found during hypoxia when the direct dilution has been used to estimate the cardiac output in men (38, 41, 44, 107, 120, 122) and calves (78).

Increased cardiac output results from an increase in both the stroke volume and the heart rate in normal man. The stroke volume increases relatively more than the heart rate (38, 41). The heart rate has been stated to increase during hypoxia in the dog but the stroke volume and slightly (68, 120). In contrast, Harrison and Blalock (34) observed only slight increase in the heart rate and large increase in the stroke volume in dogs.

The mean arterial pressure varies only slightly in man during hypoxia (34, 123). This reflects the

effect of the peripheral vasodilatation. Some variation in the mean arterial pressure is seen in hypoxia in the dog (3, 69).

The central blood volume does not change during hypoxia in man (38, 45). Measurements of central blood volume in anesthetized dogs have shown that an increase occurs (11, 61, 67, 107, 120). A large increase occurs also in the pulmonary blood volume in unanesthetized dogs during hypoxia (89).

All reports seen by the author suggest that the circulation time decreases during hypoxia. Both the arm-to-arm and lung-to-carotid appearance times decrease markedly during hypoxia in normal adult (13). A decrease in the mean transit time has been measured by the dilution method in man (from 12.3 to 10.7 sec.) (43) and in unanesthetized dogs (from 10 to 6.1 sec.) (69) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during *dn* as under severe asphyctic conditions, and in rabbits in severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions of the circulation are practically closed (40, 104). The renal blood flow almost stops in the seal and the blood flow through the abdominal aorta, kidney, and mesenteric are greatly reduced in the dog during submersion (40). The carotid arterial blood flow of the diving seal decreases considerably but remains higher than any other peripheral flow rate (40). In the submerged greyhound the coronary blood flow remains unchanged (40). Bradycardia during diving can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturate anesthesia (40).

The completeness of the peripheral vasoconstriction during *dn* is apparent from the observation that the lactic acid concentration of the peripheral blood increases only little during the *dn* but increases immediately after surfacing when the peripheral circulation is opened again (108). In addition to the cardiovascular changes there must occur reduction of the metabolic rate because the excess oxygen uptake of seals and other diving animals after the submersion period does not correspond to the calculated basal oxygen requirement during the submersion period (108). The basic reason for this lowered oxygen consumption is not known.

Although the high-output pattern may result if values are made moderately hypoxic, low-output pattern in which the cardiac output decreases abruptly for few minutes occurs during severe hypoxia in

rabbits ($pO_2 < 3$ mmHg). The arterial pressure increases gradually and there is pronounced bradycardia (74). The peripheral pressure response is mediated via sympathetic receptors and this response may be prevented by administration of dibenzylline (74). During this kind of carotid occlusion response oxygen uptake is low. The uptake returns to normal when air breathing is resumed. This pattern may also occur in dogs during hypoxia if the arterial oxygen partial pressure decreases to that observed in rabbits (less than 35 mmHg) (74).

Regulation of cardiovascular function during hypoxia

The peripheral demand for increased cardiac output during moderate hypoxia is evidently well satisfied. This is apparently due mainly to peripheral vasodilation and autonomic heart function and is evident from experimental data which show that inhibition or destruction of large part of the assumed regulation system does not seriously affect the response to hypoxia.

Already the studies of Harrison *et al.* (30) who used a technique based on the Fick principle indicated that vagotomy and administration of atropine alone or sympathectomy or ligation of both carotid and aortic nerves and bilateral atherectomy do not significantly change the hypoxic increase of the cardiac output in the dog. Göthberg *et al.* (48) also observed a normal response of the cardiac output to hypoxia after bilateral atherectomy; no response in dog isolated cerebral hypoxia and normal response during isolated trunk hypoxia (the brain being perfused with oxygenated blood).

More detailed studies have indicated the absence of neurohumoral regulation during hypoxia. Downing *et al.* (74) showed that isolated cerebral ischemia in the dog increased the heart rate, peripheral resistance and myocardial contractility. Cessation of sympathetic activity of the central nervous system followed by the occlusion of the brain blood supply resulted in a fall in cardiac output (36). All of the sympathetic chain fibers (37). The dog showed the increase in cardiac output during moderate hypoxia (80). Richardson *et al.* (103) observed that beta-adrenergic blockade in man did not reduce the increase in heart rate and cardiac output caused by hypoxia. β -adrenergic blockade in rabbits weakens the cardiac output response to hypoxia (4). Reserpine seems to have a similar effect on the heart

agents affecting beta-blockers (1,3). On the other hand, depletion of the peripheral stores of noradrenaline by reserpine did not change the cardiovascular response to mild hypoxia (21). The importance of a proper nervous regulation during maximal physical exertion was demonstrated by Donald *et al.* (32) who observed that the racing performance of grey hounds was lower after heart denervation and/or beta-adrenergic blockade.

In contrast to the evident influence of the central sympathetic system on the functions of the heart and peripheral vessels, the influence of peripheral chemoreceptors on the hypoxic circulatory regulation has been found to be of minor importance (33, 31, 9).

The type of respiratory response seems to play an important role in cardiovascular regulation. Horn (74) concluded that large lunged men and dogs with a good respiratory response to hypoxia develop the high-output pattern and small-lunged rabbits the low-output pattern. He assumes that the arterial oxygen pressure is the factor determining the type of cardiovascular response.

Strong central nervous participation is suggested by experimental data for seals which develop the low-output pattern during a normal dive but when they "know" that they can breathe through a mouthpiece any time they wish, this pattern will not occur (104). Primary central nervous regulation has also been observed during exercise: the stroke output of the heart increases at the same time when a dog begins to run without a very hemispheric haemorrhage occurring in the blood (105).

The above may be summarized by stating that increased tissue perfusion is kept at a high maximum subjected to moderate low oxygen pressure. This change is controlled mainly by local autonomic regulation in different tissues and the heart. Neurohumoral regulation provides a more appropriate distribution of blood flow and oxygen transport in the circulation in severe hypoxia. The peculiar diving pattern may be considered an expression of strong neurohumoral involvement and control in extreme hypoxia or anoxic conditions.

Hypoxia in the fetal and neonatal periods

It is of course that newborn infants and lambs are highly sensitive to moderate hypoxia. In altricial species the effect of mild hypoxia is only seen in the neonatal period but is not so pronounced in the adult because of the high tolerance of hypoxia or asphyxia in the later stages of fetal development. The fetal tolerance of hypoxia is not so high as the adult.

Tolerance of hypoxia

A distinctive characteristic of fetuses and newborn animals is their tolerance of asphyxia. The nature of this phenomenon is not exactly known. It is rather thought to be due to a lowered oxygen consumption during hypoxia in both infants (23) and lambs (1, 26). However, this decrease in later found to be due to the fact that the cool environment had lowered the oxygen consumption. Aik decreased normal above again during hypoxia (24). This decreased oxygen consumption during hypoxia does not seem to be restricted to the neonatal period, since it has been found to occur also in adult dogs (20).

Newborn mammals develop signs of oxygen debt during hypoxia. In newborn lambs the lactic acid concentration increases up to 20 mg per 100 ml during hypoxia (25). The lactic acid concentration of premature infants increases during physical activity and returns to normal afterwards, but more slowly than in adults (56). In the respiratory distress syndrome the lactic acid concentration may rise up to 15 mM, and is negatively correlated with the decreased arterial oxygen pressure (129). Infants suffering from the respiratory distress syndrome have a reduced oxygen uptake. During recovery this uptake increases first to level below normal and then returns normal again (79). Similarly the oxygen uptake seems to be high at first during positive-pressure ventilation for the resuscitation of asphyxiated infants, but falls to slightly normal limits during recovery (31).

There is no information available that could show whether newborn mammals as oxygen in hypoxia or asphyxia the conditions are mentioned above, such as long occurs in seals during diving (108).

The factors determining the tolerance of hypoxia in adults and possibly also fetuses and newborns are the respiration of the central nervous system and the heart. Oxygen deficiency seems to be the factor which limits the function of these organs rather than increased arterial dioxide levels. When subjected to severe oxygen loss, adult dogs lived 85 minutes with final partial carbon dioxide pressure of nearly 400 mmHg and blood pH of 6.5 to 6.6, but dogs breathing pure nitrogen survived only 9 minutes (73).

I computed asphyxia resulting from an occluded aorta, the myocardial glycolysis of rabbits decreases in 1 minute to minimum, also that is less than 10 per cent of the normal level (82). I think that the myocardium of the dog is no longer able to use blood glucose (47). The possibilities of anaerobic energy metabolism seem to be better in newborn rats, as the myocardium has much larger glycogen stores and higher phosphorylase content than an

adult rat heart (133). The anaerobic glycolytic activity appears to be nearly sufficient to satisfy the lower energy requirement of the brain of the newborn (39).

From the clinical standpoint it would be important if newborn could be kept in state in which its energy demands are provided by anaerobic pathway and energy is not taken from anaerobic sources which deplete glycogen stores.

Cardiovascular reactions

Many stimuli produce cardiovascular responses that indicate high degree of maturity in the newborn infant. W. Unger et al. (127) found that cardiac output and stroke volume decrease and the heart rate and peripheral vascular resistance increase in response to hypervolemia. In addition, signs of rapid change towards normalization of the blood volume are observed. Also hypervolemia induced by late cord clamping is corrected in a few hours (128). Further, more mature response of the arterial blood pressure to body tilting is observed from the fourth day after birth in normal newborn infants (45), whereas such response is not observed in premature infants (37).

The pulmonary vascular resistance increases and the arterial duct tends to reopen in neonatal lambs in arterial hypoxia (96). The same phenomena occur in newborn infants and if the aortic pressure decreases, part of the pulmonary blood flow may be directed to the aorta through the aortic duct (64). This kind of rearrangement of the circulation in severe respiratory distress has been called pulmonary hyperperfusion (22). Such change in the circulation reduces the uptake of oxygen in the lung capillaries. Only adequate ventilation and pulmonary blood flow can break this vicious circle.

The heart rate increases by 10 per cent in three minutes when infants less than six days old are subjected to an inspired oxygen content of 12 per cent (16). Short periods of hypoxia reduce the mean arterial pressure in newborn infants (64). This observation, which suggests peripheral vasoconstriction, was confirmed by Oshander and Mårdh (19) who found that strong retractor hyperemia followed the occlusion of foot and tail blood flow.

Hypoxia in neonatal lamb leads to slight reduction of the left ventricular contractility (37), peripheral vasoconstriction (117) and, in most cases, an elevated heart rate (20, 73). The data on cardiac output in hypoxic lambs differ somewhat. Cross et al. (26) did not find significant changes in this parameter; slight increase occurred in only four of ten animals. Similar results were obtained with an

rabbits ($pO_2 < 35$ mmHg). The arterial pressure increases gradually and there is pronounced bradycardia (74). The peripheral pressure response is mediated via sympathetic α -receptors and this response may be prevented by administration of dibenzylamine (74). During this kind of cardiovascular response oxygen uptake is low. The uptake returns to normal when air breathing is resumed. This pattern may also occur in dogs during hypoxia if the arterial oxygen partial pressure decreases to that observed in rabbits (less than 33 mmHg) (4).

Regulation of cardiovascular function during hypoxia

The peripheral demand for increased cardiac output during moderate hypoxia is evidently well satisfied. This is apparently due mainly to peripheral vasodilatation and autonomic heart function. It is evident from experimental data which show that inhibition or destruction of large parts of the autonomic regulation system does not seriously affect the response to hypoxia.

Already the studies of Harrison *et al.* (89) who used techniques based on the Fleck principle indicated that autonomic administration of atropine, thoracic sympathectomy, ligation of both carotid and subclavian arteries and bilateral adrenalecomy individually or in different combinations, did not significantly change the hypoxic increase of the cardiac output in the dog. G ndri *et al.* (48) also observed a normal response of the cardiac output to hypoxia after bilateral adrenalecomy; no response during isolated cerebral hypoxia and a normal response during isolated trunk hypoxia (the brain being perfused with oxygenated blood).

More detailed studies have indicated the existence of neuro-humoral regulation during hypoxia. Dowling *et al.* (34) showed that isolated cerebral ischaemia in the dog increased the heart rate, peripheral resistance and myocardial contractility. Cessation of sympathetic activity of the central nervous system following the occlusion of the brachiocephalic artery followed by decreased myocardial contractility during hypoxia (36). Ablation of the sympathetic chain from C5 to T8 in conscious dogs reduced the increase in cardiac output during moderate hypoxia (90). Richardson *et al.* (103) observed that β -adrenergic blockade in man definitely reduced the increase in heart rate and cardiac output caused by hypoxia. β -adrenergic blockade in rabbit weakens the cardiac output response to hypoxia (74). Reserpine seems to have a similar effect on the heart and

agents effecting β -blockade (1,3). On the other hand, depletion of the peripheral stores of epinephrine by syroalagopine did not change the cardiovascular response to mild hypoxia (21). The importance of a proper nervous regulation during maximal physical exertion was demonstrated by Donald *et al.* (22) who observed that the racing performance of greyhounds was lower after heart denervation and/or β -adrenergic blockade.

In contrast to the evident influence of the central sympathetic system on the functions of the heart and peripheral vessels, the influence of peripheral chemoreceptors on the hypoxic cardiovascular regulation has been found to be of minor importance (33, 34, 91).

The type of respiratory response seems to play some part in cardiovascular regulation. Barker (74) concluded that large-lunged men and dogs with a good respiratory response to hypoxia develop the high-output pattern and small-lunged rabbits the low output pattern. He assumes that the arterial oxygen pressure is the factor determining the type of cardiovascular response.

Strong central nervous participation is suggested by experimental data for animals which develop the low-output pattern during a normal life but when they "know" that they can breathe through a mouthpiece any time they wish, this pattern will not occur (108). Primary central nervous regulation has also been observed during exercise: the stroke output of the heart increases at the moment when a dog begins to run without any chemical changes occurring in the blood (108).

The above may be summarized by stating that increased tissue perfusion develops in adult mammals subjected to moderately low oxygen pressures. This change is controlled mainly by local autonomic regulation in different tissues and the heart. Neuro-humoral regulation provides a more appropriate distribution of blood flow and oxygen transport in the circulation in severe hypoxia. The peculiar diving pattern may be considered an expression of strong neuro-humoral regulatory control in extreme hypoxic or asphyctic conditions.

Hypoxia in the fetal and neonatal periods

It is obvious that newborn infants and lambs are well adjusted to meet the demands of intermittent hypoxia. The effect of arterial hypoxia on hemodynamics in the neonatal period is more complicated than in life because of the high tolerance of hypoxia in placenta and the existence of fetal shunts that are patent or can be diverted.

on the heart; when heart failure is induced by increasing the $p\text{CO}_2$ in a decapitated heart-lung preparation, the cardiac function returned to normal on infusion of epinephrine or norepinephrine. Acetyl strophanthidin also restored the cardiac function. The depressant effect of carbon dioxide on the heart in an intact organism is opposed by sympathetic discharge stimulated by direct cerebral hypercapnia. Isolated cerebral hypercapnia produces increased myocardial contractility, tachycardia and peripheral vasodilatation (34). On the other hand, both adrenergic blockade as not found by Wendling *et al.* (31) prevent the increase of cardiac output during hypercapnia. Carbon dioxide may depress myocardial function by inhibiting the citric acid cycle and by reducing the oxygen supply by γ of the Bohr shift.

The data on cardiac output during hypercapnia are contradictory. According to most reports, the cardiac output increases in man (3, 45, 82, 102, 104) and dog (18). In contrast, Auld *et al.* (10) did not find any changes in cardiac output, heart rate or peripheral resistance in anaesthetized children during hypercapnia. Winterson (121) observed both increased, decreased and unchanged cardiac outputs in human patients.

The hypercapnia that occurs at increased carbon dioxide levels in man changes the cardiac output response. In severe hypercapnia may increase cardiac output even in humans (82, 104).

Carbon dioxide usually increases the heart rate in man (102) but may cause bradycardia in the dog (2, 11). This may be a direct effect on the heart, because Downing *et al.* (34) found that isolated hypercapnia of the central nervous system of dogs results in bradycardia.

Arterial pressure increases slightly during hypercapnia. This is due to an increased cardiac output in spite of peripheral vasodilatation. Hypotension that first occurs after experimental hypercapnia (110) is most pronounced after the arterial $p\text{CO}_2$ has exceeded 80 mmHg.

Tolerance of high $p\text{CO}_2$ seems to be good in dogs provided that oxygenation is sufficient. Nakayama *et al.* (91) observed an increase in cardiac output 61 per cent and marked bradycardia (38 per cent decrease) after 15 minutes of pure oxygenation at 14, 150 mmHg. The mean arterial pressure in these animals was 1.5 as long as 60 minutes in dogs (14, 150 mmHg, 11 mmHg) and blood pH of 6.5.

Cardiac disturbances, extrapulmonary, legnary abnormal (renal and renal artery) and even extracardiac (pulmonary) have been observed in man during hypercapnia. The disturbances have been

attributed to increased serum potassium concentration (70) but this explanation has not been generally accepted (90).

Hypercapnia during the fetal and neonatal periods

Intrauterine asphyxia consists partly of hypercapnia. The influence of isolated hypercapnia in human fetuses has not been investigated. Ansell *et al.* (9) ventilated pregnant ewes with carbon dioxide and found that the arterial $p\text{CO}_2$ increased, the arterial blood pressure rose and the carotid, femoral and umbilical blood flow increased in the fetuses. These changes possibly indicate an increased cardiac output.

Increased cardiac output has been observed in neonatal lambs during hypercapnia; also the heart rate and central blood volume are elevated (72, 117). Hypercapnia does not, however, alter the state of the arterial duct (86).

EFFECTS OF METABOLIC ACIDOSIS ON THE BLOOD CIRCULATION

The cardiac output is low in dogs suffering from metabolic acidosis (14, 48) but Bokros (104) and Richardson *et al.* (103) did not find changes in cardiac output in men after infusion of small amounts of lactic or hydrochloric acid. Richardson *et al.* observed an increased cardiac output in men after the infusion of sodium bicarbonate.

A decreased cardiac output has been attributed to decreased myocardial contractility in dogs suffering from metabolic acidosis (27). The heart function slows down less in intact animals than in isolated hearts (48, 93). However, metabolic acidosis does not significantly alter the cardiac function in full-grown rats (4) and newborn lambs (37) after external surgery.

The greater acidity of an intact organism withstands low pH is thought to be due to the function of the sympathetic nervous system. However, Downing *et al.* (36) observed an increased cardiac function when the cerebral blood supply was interrupted. They concluded that lower sympathetic centers regulate heart function. This view is substantiated by the observation that lactic acid infusion usually produces bradycardia and increased arterial pressure corresponding to that produced by the injection of 2 $\mu\text{g/kg}$ of epinephrine; these responses are no longer obtained after the removal of the adrenals (127).

Acidosis may decrease myocardial function by diminishing carbohydrate uptake (48, 93) or may lower the oxygen affinity of the myocardium.

ketonmagnetic flowmeter for newborn calves with normal acid base balance (103) and for neonatal lambs with normal acid base balance when the dye dilution method was used (11). In contrast the preliminary results of Koiikko (7) show that cardiac output increases during moderate hypoxia in neonatal lambs when acid base conditions are normal.

The central blood volume increases in neonatal lambs during hypoxia according to preliminary results of Koiikko (). More recently Stahlman *et al* (117) measured pulmonary blood volumes by the slope method and reported decreased volume during hypoxia.

There are data which indicate that the living pattern may occur also in fetuses and newborn infants. Bradycardia which may be due to brain compression and reduced cerebral blood flow is observed in human fetuses during uterine contractions (8). Bradycardia continues to go than the uterine contraction period in asphyxiated fetuses. This bradycardia may be prevented with atropine (57). Also the diving bradycardia of seals is prevented by this drug (40). This is the acid concentration of the blood of human infants remains low during delivery but increases immediately afterwards (63, 1). This variation of the lactate concentration during and after delivery may reflect peripheral vasoconstriction similar to that observed in diving animals. According to Colander (90) breathing of gas mixtures containing less than 13 per cent oxygen produces a decreased blood flow in the limbs and in the heart at the same time in infant but then, for a while, pronounced bradycardia. This kind of adjustment of the peripheral circulation requires a more centrally controlled vasoconstriction. Already at this age the peripheral vascular bed contracts on infusion of norepinephrine (69).

Hypoxia or asphyxia in fetal lambs at term leads to increased arterial pressure, bradycardia, and decreased femoral arterial and increased carotid and umbilical arterial blood flows (8). Elber *et al* (40) observed a diving pattern in neonatal calves, but not before the 10th day of life.

Effects of acid base changes on the response to hypoxia

The cardiac output of newborn calves increases in hypoxia when the animal has metabolic alkalosis. The output returns to normal when the acid base abnormality and hypoxemia are corrected (103). Similar results were obtained by Koiikko () for newborn lambs. As found by Downing *et al* in calf (36) and newborn lambs (37) the decrease seems to

be due to decreased myocardial contractility in these conditions. In the experiment of Downing *et al* hypoxia or acids alone did not depress the myocardial contractility significantly but the combined effect of these conditions was a markedly depressed ventricular function. This depression was less in newborn lambs than in adult cats, which possibly indicates a better anaerobic capacity in the former.

The reason for the decreased myocardial contractility is not clear. The factors maintaining the contractility require an adequate supply of oxygen and glucose for the energy metabolism of the heart and proper function of the sympathetic nervous system. In addition, in respiratory as well as metabolic the Bohr shift may decrease the myocardial oxygen supply. In severe asphyxia the myocardial glycogen stores may be depleted entirely and the ability to utilize blood glucose may be reduced (4). The central nervous system has a certain regulatory effect on the myocardial contractility. According to Donald *et al* (30) occlusion of the cerebral blood flow during hypoxia associated with metabolic acidosis causes a further decrease in myocardial contractility.

CARDIOVASCULAR ADJUSTMENTS DURING ACUTE HYPERCAPNIA

Hypercapnia in adults

Carbon dioxide removal is not impaired by a moderate decrease in cardiac output (34). This may be explained by an effective transport of carbon dioxide to the lungs. In spite of the small potential danger of carbon dioxide retention, the carbon dioxide level seems to be a very strong regulator of both local and central circulation. The quick changes in ventilation and circulation seen in hypercapnia tend to normalize the acid base conditions. The main sites where carbon dioxide exert its effects are the arterioles, the heart, the adrenals, and the chemoreceptors of the aorta, carotid sinuses and brain.

Carbon dioxide generally induces dilatation of the arterioles. This effect is particularly strong in the cerebral circulation, but seems to be weaker in the coronary circulation (106).

Carbon dioxide has a depressant effect on an isolated heart (99). Boissac and Broza (13) observed that entilation of 3 to 50 per cent carbon dioxide in the heart dogs resulted in a 15 to 50 per cent decrease in the ventricular contractile force. The response to carbon dioxide has often been attributed to the reflexes after less cardiac output. A Leonard *et al* () has used Ca^{++} (97) the reason for this seems to be increased sympathetic stimulation.

on the heart; when heart failure was induced by increasing the $p\text{CO}_2$ in decervated heart lung preparation, the cardiac function returned to normal on infusion of epinephrine or norepinephrine. Acetyl strophanthidin also restored the cardiac function. The depressant effect of carbon dioxide on the heart is an intact organism is opposed by sympathetic discharge stimulated by direct cerebral hypercapnia. Isolated cerebral hypercapnia produces increased myocardial contractility (tachycardia and peripheral vasoconstriction) (34). On the other hand, beta-adrenergic blockade was not found by Wendling *et al.* (131); prevent the increase of cardiac output during hypercapnia. Carbon dioxide may depress myocardial function by inhibiting the citric acid cycle and by reducing the oxygen supply by 1/3 of the Bohr shift.

The data on cardiac output during hypercapnia are contradictory. According to most reports, the cardiac output increases in man (8, 43, 83, 102, 104) and dog (18). In contrast, Dahl *et al.* (10) did not find any changes in cardiac output, heart rate or peripheral resistance in anesthetized children during hypercapnia. Henttinen (127) observed both increased, decreased and unchanged cardiac outputs in human pale dogs.

The hyperventilation that occurs at increased carbon dioxide levels may change the cardiac output response, but the hyperventilation may increase cardiac output even in pale dogs (84, 104).

Carbon dioxide usually increases the heart rate in man (104) but may cause bradycardia in the dog (94, 121). This may be direct effect on the heart, because Downing *et al.* (34) found that isolated hypercapnia in the central nervous system of dog results in tachycardia.

Arterial pressure increases slightly during hypercapnia. This is due to an increased cardiac output in spite of peripheral vasoconstriction. Hypotension that often occurs after experimental hypercapnia (110) is most pronounced after the arterial $p\text{CO}_2$ has exceeded 50 mmHg.

Tolerance of high $p\text{CO}_2$ seems to be good in dogs provided that oxygenation is sufficient. Vahanian *et al.* (91) observed increase in cardiac output (67 per cent) and marked bradycardia (28 per cent decrease) after 15 minutes of partial oxygenation (1/3 O_2) of 120 mmHg. The survival time in these conditions may be as long as 60 minutes in dogs with $p\text{CO}_2$ of nearly 400 mmHg and blood pH of 6.5 (44, 73).

conduction disturbances, extrasystoles, irregular abnormal atrial and nodal activity (31) and even ventricular fibrillation (17) have been observed in man during hypercapnia. The latter may be due to

attributed to increased serum potassium concentration (78) but this explanation has not been generally accepted (89).

Hypercapnia during the fetal and neonatal periods

Intrauterine asphyxia consists partly of hypercapnia. The influence of isolated hypercapnia in human fetuses has not been investigated. Anelli *et al.* (8) intubated pregnant ewe with carbon dioxide and found that the arterial $p\text{CO}_2$ increased, the arterial blood pressure rose and the carotid, femoral and umbilical blood flow increased in the fetuses. These changes possibly indicate an increased cardiac output.

Increased cardiac output has been observed in neonatal lambs during hypercapnia; also the heart rate and central blood volume are elevated (117). Hypercapnia does not, however, alter the state of the arterial duct (90).

EFFECTS OF METABOLIC ACIDOSIS ON THE BLOOD CIRCULATION

The cardiac output is low in dogs suffering from metabolic acidosis (13, 49) but Roberts (104) and Richardson *et al.* (102) did not find changes in cardiac output in men after infusion of small amounts of lactic or hydrochloric acid. Richardson *et al.* observed an increased cardiac output in men after the infusion of sodium bicarbonate.

A decreased cardiac output has been attributed to decreased myocardial contractility in dogs suffering from metabolic acidosis (27). The heart function slows down less in intact animals than in isolated heart (49, 51). However metabolic acidosis does not significantly alter the ventricular function in full-grown cats (36) and newborn lambs (37) after extensor surgery.

The greater ability of an intact organism to withstand low pH is thought to be due to the function of the sympathetic nervous system. However Downing *et al.* (34) observed an increased ventricular function when the central blood supply was interrupted. They concluded that lower sympathetic centers begin to function. This view is substantiated by the observation that lactic acid infusion usually produces tachycardia and increased arterial pressure corresponding to that produced by the injection of 2 $\mu\text{g/kg}$ of epinephrine; these responses are no longer obtained after the removal of the adrenals (137).

Acidosis may suppress myocardial function by diminishing carbohydrate uptake (48, 94) or may lower the oxygen supply to the myocardium by

electromagnetic flowmeter for newborn calves with normal acid base balance (10.) and for neonatal lambs with normal acid base balance when the dye dilution method was used (11.) In contrast the preliminary results of Kolvikko (72) show that cardiac output increases during moderate hypoxia in neonatal lambs when acid base conditions are normal.

The central blood volume increases in neonatal lambs during hypoxia according to preliminary results of Kolvikko (72) More recently Stahlman *et al.* (117) measured pulmonary blood volumes by the slope method and reported decreased values during hypoxia.

There are data which indicate that the diving pattern may occur also in fetuses and newborn infants. Bradycardia which may be due to brain compression and reduced cerebral blood flow is observed in human fetuses during uterine contractions (87) Bradycardia continues longer than the uterine contraction period in asphyxiated fetuses. This bradycardia may be proved true with opiate (87) Also the diving bradycardia of seals is proved by this drug (40) The lactic acid concentration of the blood of human infants remains low during delivery but increases immediately after respiration (63-71) This variation of the lactic acid concentration during and after delivery may reflect peripheral vasoconstriction similar to that observed in diving animals. According to Celandier (20) breathing of gas mixtures containing less than 15 per cent oxygen produces a decreased blood flow in the limbs and tachycardia at the same time in infants but then, for a while, pronounced bradycardia. This kind of adjustment of the peripheral circulation requires a mature centrally controlled vasoconstriction. Already at this age the peripheral vascular bed contracts on infusion of norepinephrine (69)

Hypoxia or asphyxia in fetal lambs at term leads to increased arterial pressure, bradycardia, and decreased femoral arterial and increased carotid and umbilical arterial blood flow (8) Elsnic *et al.* (40) observed a diving pattern in neonatal calves, but it before the 10th day of life.

Effects of acid base changes on the response to hypoxia

The cardiac outputs of newborn calves decrease in hypoxia when the animals have metabolic acidosis. The output reverts to normal when the acid base abnormality and hypoxemia are corrected (10.) Similar results were obtained by Kolvikko (73) for newborn lambs. As found by Downing *et al.* in cats (36) and newborn lambs (37) the decrease seems to

be due to decreased myocardial contractility in these conditions. In the experiments of Downing *et al.*, hypoxia or acidemia alone did not depress the myocardial contractility significantly but the combined effect of these conditions was a markedly depressed atricular function. This depression was less in newborn lambs than in adult cats, which possibly indicates a better reserve capacity in the former.

The reason for the decreased myocardial contractility is not clear. The factors maintaining the contractility are an adequate supply of oxygen and glucose for the energy metabolism of the heart and proper function of the sympathetic nervous system. In acidosis, in respiratory as well as in metabolic, the Bohr shift may decrease the myocardial oxygen supply. In severe asphyxia the myocardial glycogen stores may be depleted entirely and the ability to utilize blood glucose may be reduced (47) The central nervous system has certain regulatory effect on the myocardial contractility. According to Downing *et al.* (36) occlusion of the cerebral blood flow during hypoxia associated with metabolic acidosis causes a further decrease in myocardial contractility.

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Hypercapnia in adults

Carbon dioxide removal is not impaired by a moderate decrease in cardiac output (54) This may be explained by an effective transport of carbon dioxide to the lungs. In spite of the small potential danger of carbon dioxide retention the carbon dioxide level seems to be a very strong regulator of both local and general circulation. The quick changes in ventilation and circulation seen in hypercapnia tend to normalize the acid base conditions. The main sites where carbon dioxide exerts its effects are the arterioles, the heart, the adrenals, and the chemoreceptors of the aorta, carotid sinuses and brain.

Carbon dioxide generally induces dilatation of the arterioles. This effect is particularly strong in the cerebral circulation, but seems to be weaker in the coronary circulation (100)

Carbon dioxide has a depressant effect on an isolated heart (99) Bonifacio and Brown (15) observed that entilation of 5 to 50 per cent carbon dioxide by open-chest dogs resulted in a 15 to 50 per cent decrease in the atricular contractility. The response to carbon dioxide has often been observed to be the reverse after less external surgery. As demonstrated by Natus and Cartwright (93) the reason for this seems to be an increased sympathetic activity.

The Aims of the Study

The aims of the present study were to determine

— the basal values of the cardiac output, heart rate, stroke volume, central blood volume, the ratio of stroke volume to central blood volume and the circulation time in sheep from birth to the age of one year
— the influence of chloralose anaesthesia on the blood circulation of neonatal lambs and their cardiovascular responses to hypoxia and hypercapnia,

— the cardiovascular response of neonatal lambs and, for comparison, sheep up to the age of one year to acute arterial hypoxia,
— the influence of metabolic acidosis on the cardiovascular response of neonatal lambs to hypoxia,
— the circulatory response of neonatal lambs and sheep to hypercapnia,
— the influence of metabolic actions on cardiovascular functions in newborn lambs.

limit the formation of oxyhemoglobin. A high acidity does not seem to depress the myocardial response to infused norepinephrine (35).

The effect of metabolic acidosis seems to have been investigated less in the fetal and neonatal periods than later in life. Metabolic acidosis produced by lactic acid infusion decreases cardiac output in newborn calves; correction of the acid-base status with bicarbonate raises the cardiac output to normal again (103). Treatment of infants suffering from respiratory distress with alkali and glucose (124) has been observed to decrease mortality (1,5). The same treatment improves the cardiovascular functions of newborn monkeys suffering from experimental asphyxia (2).

EFFECTS OF CHLORALOSE ANESTHESIA ON THE CIRCULATION

Chloralose is commonly considered one of the best anesthetics in circulation studies. However, it has

been observed to increase the heart rate by 40 per cent and to correct respiratory and other sinus arrhythmias (80). v. Luedy considered that there is a synergism between chloralose and epinephrine with it however presenting a very direct evidence for his statement (80).

Shabetai *et al.* (114) observed that chloralose may change the cardiac output by 25 to 40 per cent. In contrast Wiggers (133) reported no changes in cardiac output following the administration of chloralose.

Chloralose has been the agent most commonly used to produce general anesthesia in newborn lambs. Cross *et al.* (20) observed that newborn lambs need considerably less of this agent than older sheep for sufficient anesthesia.

On the basis of extensive studies of hypoxia in rabbits, Korner (73) pointed out the importance of not using anesthetics during experimental hypoxia, because anesthesia greatly alters the effect of hypoxia on the circulation of these animals.

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- the cardiovascular response of neonatal lambs and, for comparison, sheep up to the age of one year to acute arterial hypoxia,
- the influence of metabolic acidosis on the cardiovascular response of neonatal lambs to hypoxia,
- the circulatory response of neonatal lambs and sheep to hypercapnia,
- the influence of metabolic acidosis on cardiovascular functions in newborn lambs.

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The effect of metabolic acidosis seems to have been investigated less in the fetal and neonatal periods than late in life. Metabolic acidosis produced by lactic acid infusion decreases cardiac output in newborn calves; correction of the acidosis at this time with bicarbonate raises the cardiac output to normal again (103). Treatment of infant suffering from respiratory distress with alkali and glucose (14) has been observed to decrease mortality (1-5). The same treatment improves the cardiovascular function of newborn monkeys suffering from experimental asphyxia (4).

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Shahbatal *et al.* (11) observed that chloralose may change the cardiac output by 25 to 10 per cent. In contrast Wiggers (133) reported no changes in cardiac output following the administration of chloralose.

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On the basis of extensive studies of hypoxia in rabbits, Horner (73) pointed out the importance of not using anesthesia during experimental hypoxia because anesthesia greatly alters the effect of hypoxia on the circulation in these animals.

TABLE III The animals used in the present study and the experiments done on them

	Number of animals	Age means and range	Anesthetized	Unanesthetized	Respirator used
Whole series	67				
Rejected cases	13				
Qualified cases	34				
Lambs	43	3.0 day (1.3—4.3)	25	17	
Hypoxia	—	4.0 days (1.3—5.0)	16	9	7
— group A	10	7.2 days 1.3—5.0)	3	3	3
— group B	11	6.0 day —14	8	3	3
— group C	4	3.1 days (1.3—7)	3	1	1
Hyper. pneumonia	14	6.0 day (1.3—4)	8	6	4
M. tuberculosis acidophile	9	4.9 day 1.3—9	9	1	
Sheep	9	9.0 months (6—1)	1	8	
Hypoxia	6		1	6	
Hyperpnea	3			3	

Four related to the ventilated ⑥
 isolated with ventilated ②

Material

Sixty-seven lambs and sheep were employed in the present study. Of these, 13 animals were rejected later on various grounds which included death during an experiment, technical errors in dye dilution recordings, poor condition of the animal and abnormal cardiovascular patterns. Qualified results were thus obtained from 54 animals (Table III).

At the beginning of each experiment the basal circulatory values were determined. At this moment the animals had to be in good condition with a normal acid-base status ($p\text{CO}_2$ 40 ± 5 mmHg and BE ± 3 meq/l) and without any signs of fetal shunts in the dye curves. Also cardiac arrhythmias (as, for example, in the case presented in Fig. 18) led to exclusion from the series.

LAMBS

The number of lambs was 45 of which 23 were females and 22 males. The age distribution is presented in Table III. Lambs less than 36 hours old were not used in order to avoid fetal shunts. All of the lambs had been delivered vaginally and were apparently in good condition. The following experiments were carried out on the lambs.

Hypoxia experiments were conducted with 25 animals. The animals were divided into three groups according to the degree of metabolic acidosis that developed. Group A

comprised those with a base excess (BE) from 0 to -5 meq/l, group B those with a BE from -5 to -10 meq/l and group C those with a BE less than -10 meq/l. The age distribution is shown in Table III.

Hypercapnia was induced in 14 animals qualified for the analysis of the response. The cases presented in Figs. 17 and 18 were excluded because of cardiac arrhythmias.

Metabolic acidosis developed in 9 lambs so that it was possible to follow its progress by determining acid-base values.

A respirator was used in some hypoxia experiments to counteract the effect of hyperventilation on $p\text{CO}_2$. It was used also in 4 hypercapnia experiments to produce higher carbon dioxide levels in the arterial blood and prevent hyperventilation. If a lamb was in such a condition that it required a respirator it was excluded from the series.

SHEEP

The term sheep as used here refers to animals from 6 to 12 months old. Of the 9 sheep studied, 4 were females and 5 males. Anaesthesia was induced with chloralose in one case, mild sedation with Sombutol® in 4 cases, and no sedation in 4 cases. Hypoxia and hypercapnia experiments were carried out on the sheep. Metabolic acidosis did not develop in any of the sheep.

TABLE III The animals used in the present study and the experiments done on them

	Number of animals	Age mean and range	Anaesthesia	Exposure to the flood	Respirator used
Whole series	67				
Rejected ones	12				
Qualified ones	55				
Lambs	45	3.0 day (1.5-4.5)	4	17	
Hypocis	5	6.0 day (1.5-20)	16	9	7
— group A	10	7.2 days (1.5-20)	5	3	3
— group B	11	6.0 days (2-14)	8	3	3
— group C	4	3.1 day (1.5-7)	5	1	1
Hypertrophic	14	6.0 day (1.5-8)	8	6	4
Metabolic acholus	9	4.9 day (1.5-9)	6	1	
Sheep	9	8.0 months (6-11)	1	6	
Hypoxia	6		1	6	
Hypertrophic	3			3	

Four related to homologous

related to homologous

Material

Sixty-seven lambs and sheep were employed in the present study. Of these, 13 animals were rejected later on various grounds which included death during an experiment, technical errors in dye dilution recordings, poor condition of the animal and abnormal cardiovascular patterns. Qualified results were thus obtained from 54 animals (Table III).

At the beginning of each experiment the basal circulatory values were determined. At this moment the animals had to be in good condition with a normal acid-base status ($p\text{CO}_2$ 40 ± 5 mmHg and $\text{BE} \pm 3$ meq/l) and without any signs of fetal shunts in the dye curves. Also cardiac arrhythmias (as, for example, in the case presented in Fig. 18) led to exclusion from the series.

LAMBS

The number of lambs was 45 of which 23 were females and 22 males. The age distribution is presented in Table III. Lambs less than 36 hours old were not used in order to avoid fetal shunts. All of the lambs had been delivered vaginally and were apparently in good condition. The following experiments were carried out on the lambs.

Hypoxia experiments were conducted with 20 animals. The animals were divided into three groups according to the degree of metabolic acidosis that developed. Group A

comprised those with a base excess (BE) from 0 to -5 meq/l, group B those with a BE from -5 to -10 meq/l and group C those with a BE less than -10 meq/l. The age distribution is shown in Table III.

Hypercapnia was induced in 14 animals qualified for the analysis of the response. The cases presented in Figs. 17 and 18 were excluded because of cardiac arrhythmias.

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A respirator was used in some hypoxia experiments to counteract the effect of hyperventilation on $p\text{CO}_2$. It was used also in 4 hypercapnia experiments to produce higher carbon dioxide levels in the arterial blood and prevent hyperventilation. If a lamb was in such a condition that it required a respirator it was excluded from the series.

SHEEP

The term sheep as used here refers to animals from 6 to 12 months old. Of the 9 sheep studied 4 were females and 5 males. Anaesthesia was induced with chloralose in one case, mild sedation with Sombuto[®] in 4 cases, and no sedation in 4 cases. Hypoxia and hypercapnia experiments were carried out on the sheep. Metabolic acidosis did not develop in any of the sheep.

Hypercapnia was induced by ventilation with air containing 10 per cent carbon dioxide through the face mask or respirator.

Dye dilution curves were recorded at intervals of 1 to 5 minutes during the experiments.

The removed blood samples were as small as possible. The total blood removed from a lamb varied from 5 to 1 ml and was replaced with saline or with blood from the ewe. The blood removed from the sheep was considered so small in volume that it was not replaced.

DYE DILUTION EQUIPMENT AND PROCEDURES

For the recording of the dye dilution curves, a densitometer-preamplifier system was designed and built. A reflecting instrument for the measurement of absorption at a wavelength of 805 nm (manufactured by Hipp & Zonen) was modified into a transmittance densitometer. A special preamplifier was built to obtain a linear relationship between dye concentration and pen deflection. This preamplifier was a long-tailed pair amplifier. The input impedance of the preamplifier was adjusted so that a nearly linear response was obtained for dye concentration up to 10 mg per liter. By matching the transistors carefully it was possible to reduce the drift to less than ± 0.5 per cent of the full-scale deflection per minute when the densitometer tracing was being recorded. To remove high frequency disturbances from the dye curve a filter was connected at the input of the preamplifier. This made the system slightly sluggish; the 95 per cent response time for sudden changes in densitometer output was 0.22 to 0.4 seconds. To minimize the sluggishness of the response the figure of merit of the sampling catheter was held at less than 0.4 seconds. The total volume of the catheter and cuvette was 0.5 ml. The blood

was drawn through them at a constant rate of 39 ml per minute. The catheter transit time was 0.6 seconds. The 90 per cent response time for a square wave was 1.0 second. The system was very sensitive to flow rate; the change in deflection caused by a change in flow from 0 to 39 ml per minute was at most 90 per cent of the full-scale deflection.

The blood was withdrawn through the densitometer cuvette with an Atlas constant speed withdrawal-infusion pump which drew water from the lower end of a chamber which caused blood to flow onto a rubber diaphragm within the chamber. The amount of blood withdrawn from the lambs was about 1.5 ml and that withdrawn from the sheep up to 30 ml. The blood was returned to the artery and the blood loss was practically nil.

The dye dilution apparatus was calibrated with 10 ml of arterial blood containing 0.065 mg of Cario-Green[®]. This blood was drawn through the cuvette from a syringe at a rate of 39 ml per minute. The base line was obtained by passing arterial blood through the cuvette from another syringe. The calibration was done in duplicate on two occasions during the series of experiments with each animal. The separate calibration readings usually agreed very well with each other.

Solutions of Cario-Green[®] containing 1.25 or 2.5 mg of the dye per ml were injected. Amounts of 0.06 to 0.08 mg of dye per kg of body weight were sufficient to produce good curves. The injected volume did not exceed 1 ml.

The recording of the dye dilution curves was done with a Sanborn recorder (model 150) connected to an AC/DC preamplifier (model 140-1000). The maximal deflection obtained with this recorder was only 50 mm which was found somewhat troublesome because overshooting occurred or curves of low amplitude resulted.

Carlo Green[®] (Hyscon, Westcott & Denning, Inc., Baltimore, Maryland)

Methods

PREPARATION

The preparation of the animals was usually begun with the insertion of catheters under local Anestecain[®] anesthesia one catheter was inserted into a femoral artery and further to a point close to the aortic bifurcation for withdrawing blood through a densitometer and two catheters were inserted into the superficial jugular vein until they entered the right atrium one for injection of dye solution and the other for infusion of other solutions. The actual locations of the catheter tips were controlled at autopsy. To prevent coagulation of blood in the catheters, 1 ml of heparin was injected into the latter at intervals of 1 to 2 hours.

When general anesthesia was induced, chloralose 20 to 50 mg/kg was injected into a major vein of the lamb. The anesthesia was maintained as light as possible but shivering was suppressed. General anesthesia was given to all lambs which were to be subjected to tracheotomy and artificial respiration in order to avoid vagal blocks. Lambs not subjected to general anesthesia usually remained calm sucking the finger of one of the team members was often sufficient to calm an animal. However the animals were sometimes restless during periods of hypoxia and hypercapnia.

Administration of Sombutol[®] (1 to 4

Anestecain[®] (Lidocaine) manufactured by Läkko Or Turku Finland

Sombutol[®] (mephramine 0.030 mephramine 0.0072, urethane 0.050 pfr ft. 0.130 glyce of 0.15 phle ycarbinol 0.015 per ml) manufactured by Läkko Oy Turku, Finland.

mg/kg of barbiturate) was used to produce a mild sedation in some of the sheep. Formation of gas in the stomach and intestines was so strong in some of the sheep that puncture with a large needle was necessary to prevent difficulty in breathing.

To prevent a spontaneous fall in body temperature the lambs were placed on a warm plate. The temperatures of animals were controlled with electronic equipment using rectal electrodes (manufactured by Elektrolaboratoriet, Copenhagen). The temperatures of the animals varied between 39 and 41 C but variations exceeding 1 C did not occur in any animal. Slight decreases in temperature occurred in the hypoxia experiments.

Needle electrodes were used when recording ECG's with a Sanborn four-channel recorder (model 150) connected to an ECG preamplifier. The paper speed of 15 or 5 mm per second used to record the dye curves was sufficient to permit calculation of the heart rate and to detect gross abnormalities in cardiac rhythm.

EXPERIMENTS

Hypoxia was induced by ventilating the lambs with 10 per cent oxygen in nitrogen through a mask applied to the nose. When a respirator (manufactured by C. F. Palmer London) was used, the gas mixture was administered through it. In the experiments with the sheep tracheotomy was not done nor was the respirator used the gas mixture was supplied through a mask.

Hyperventilation was induced by ventilation with air containing 10 per cent carbon dioxide through the face mask or respirator.

Dye dilution curves were recorded at intervals of 1 to 5 minutes during the experiments.

The removed blood samples were as small as possible. The total blood removed from a lamb varied from 5 to 15 ml and was replaced with saline or with blood from the ewe. The blood removed from the sheep was considered so small in volume that it was not replaced.

DYE DILUTION EQUIPMENT AND PROCEDURES

For the recording of the dye dilution curves, a lensometer preamplifier system was designed and built. A reflecting instrument for the measurement of absorption at a wavelength of 805 nm (manufactured by Kipp & Zonen) was modified into a transmittance densitometer. A special preamplifier was built to obtain a linear relationship between dye concentration and pen deflection. This preamplifier was a long-tailed-pair amplifier. The input impedance of the preamplifier was adjusted so that a nearly linear response was obtained for dye concentration up to 10 mg per liter. By matching the transistors carefully it was possible to reduce the drift to less than ± 0.5 per cent of the full-scale deflection per minute when the lensometer tracing was being recorded. To remove high frequency disturbances from the dye curve a filter was connected at the input of the preamplifier. This made the system slightly sluggish; the 93 per cent response time for sudden changes in densitometer output was 0.22 to 0.4 seconds. To minimize the sluggishness of the response the figure of merit of the sampling catheter was held at less than 0.4 seconds. The total volume of the catheter and cuvette was 0.5 ml. The blood

was drawn through them at a constant rate of 39 ml per minute. The catheter transit time was 0.6 seconds. The 90 per cent response time for a square dye wave was 1.0 seconds. The system was very sensitive to flow rate; the change in deflection caused by a change in flow from 0 to 39 ml per minute was at most 20 per cent of the full-scale deflection.

The blood was withdrawn through the densitometer cuvette with an Atlas constant speed withdrawal-infusion pump which drew water from the lower end of a chamber which caused blood to flow onto a rubber diaphragm within the chamber. The amount of blood withdrawn from the lambs was about 10 ml and that withdrawn from the sheep up to 30 ml. The blood was returned to the artery and the blood loss was practically nil.

The dye dilution apparatus was calibrated with 10 ml of arterial blood containing 0.0625 mg of Carbo-Green[®]. This blood was drawn through the cuvette from a syringe at a rate of 39 ml per minute. The base line was obtained by passing arterial blood through the cuvette from another syringe. The calibration was done in duplicate on two occasions during the series of experiments with each animal. The separate calibration readings usually agreed very well with each other.

Solutions of Carbo-Green[®] containing 1.5 or .5 mg of the dye per ml were injected. Amounts of 0.06 to 0.08 mg of dye per kg of body weight were sufficient to produce good curves. The injected volume did not exceed 1 ml.

The recording of the dye dilution curves was done with a Sanborn recorder (model 150) connected to an A.C. preamplifier (model 150-1000). The maximal deflection obtained with this recorder was only 50 mm, which was found somewhat troublesome because overshooting occurred on curves of low amplitude resulted.

[®]Carbo Green (H) Inc., Westcott & Dunlop, Inc. Baltimore, Maryland)

OTHER MEASUREMENTS

The variation of the arterial oxygen saturation during the hypoxia experiments was followed by measuring it in duplicate samples with a Brinkman hemoreflexor (Kipp & Zonen)

Acid base changes were followed by taking samples from the femoral artery at frequent intervals during the experiments, especially during the hypercapnia periods. These were sealed in airtight syringes. The actual pH, actual $p\text{CO}_2$, standard bicarbonate level and base excess were measured as proposed by Siggaard Andersen *et al* (113) and Siggaard Andersen and Engel (114) within 1 to 2 hours of sampling

CALCULATIONS

The recorded dye dilution curves were accepted for calculations when there were no signs of marked shunts in any direction and when signs of recirculation were noted after the descending limb of the curve had fallen below 50 per cent of the maximum amplitude of the curve (60)

Signs of small right to-left or left to-right shunt flows were noted in the youngest lambs. These were ignored when it was apparent that the errors could not exceed 5 per cent

The cardiac outputs (CO) were calculated from the Stewart-Hamilton equation

$$\text{CO} = \frac{60 \text{ I}}{\bar{c} \cdot t}$$

in which I is the amount of dye injected (mg), \bar{c} the mean concentration of dye (mg per liter) during the primary curve and t the duration of the primary curve in seconds. $\bar{c} \cdot t$ was obtained by measuring the area under the primary curve with a planimeter and dividing the area by a calibration factor

The primary curve was separated from the recirculation wave in the normal way by extrapolating the declining slope on semi-logarithmic paper

The heart rate was calculated from ECG tracings which were recorded at the same time as the dye dilution curves on the same paper

The stroke volume was obtained by dividing the cardiac output by the heart rate

The appearance time was obtained by subtracting the catheter transit time (0.6 seconds) from the recorded appearance time

The mean transit time (MTT) was calculated according to Hamilton (56) and Meier (86)

$$\text{MTT} = \frac{\sum c \cdot t}{\sum c}$$

The central blood volume (CBV) was calculated from

$$\text{CBV} = \text{CO} \cdot \text{MTT}$$

The relationship between the appearance time and the ratio of central blood volume to the cardiac output can be easily investigated by comparing AT and MTT. The assumed relationship may be expressed by

$$\text{AT} = \frac{k \cdot \text{CBV}}{\text{CO}}$$

On substituting $\text{CBV} = \text{CO} \cdot \text{MTT}$ in this equation it follows that

$$\text{AT} = k \cdot \text{MTT}$$

Thus a linear relationship must exist between AT and MTT if the initial assumption is valid

The statistical treatment of the data was done by applying Student's t test. Regression lines were fitted to the data with an IBM 1130 computer. A difference was considered almost significant when $p < 0.05$, significant when $p < 0.01$ and highly significant when $p < 0.001$

TESTS OF THE DYE DILUTION EQUIPMENT

The linearity of the densitometer-transducer response was tested with known amounts of Cariblo-Green[®] in blood. The results are presented in Fig. 1. The linearity was satisfactory up to a dye concentration of 10 mg per liter. The logarithmic and linear responses are also presented in Fig. 1. It will be seen that the response curve of the apparatus deviates from linearity 8 per cent at a dye concentration of 10 mg per liter. In practice the height of the curve usually corresponded to from 4 to 8 mg of dye per liter and never exceeded 10 mg per liter.

The dye dilution apparatus was tested with an artificial flow system using volumes of 50 to 140 ml. The flow through this system could be calculated with an error of less than ± 1

per cent as illustrated in Fig. 2. The accuracy of the flow measurements was independent of the volume of the artificial system. The flow rate in a tube 1400 ml in volume could be measured with the same accuracy.

Volume measurements in the range from 50 to 140 ml in the artificial flow system did not give satisfactory results, because of uneven distribution of the dye. However, the volume of a plastic tube of 1400 ml capacity could be measured with satisfactory accuracy. The errors were less than ± 10 per cent. The dye dilution apparatus was thus considered sufficiently accurate for measurements of both flow rate and volume.

Duplicate determinations of carotid output with lambs in a steady state showed that the maximum error was ± 1 per cent and ± 10 per cent.

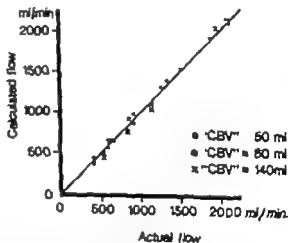
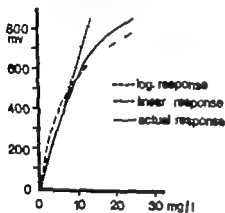


Fig. 1 (left): The response of the densitometer to changes in the dye concentration of whole blood (milk base). The logarithmic (broken line) and linear (dash-dot line) responses are also drawn.

Fig. 2 (right): The reproducibility of flow measurements with the dye dilution equipment in an artificial flow system using water as medium. The results obtained using different volumes are indicated by different symbols.

OTHER MEASUREMENTS

The variation of the arterial oxygen saturation during the hypoxia experiments was followed by measuring it in duplicate samples with a Brinkman hemoreflector (Hipp & Zonen).

Acid-base changes were followed by taking samples from the femoral artery at frequent intervals during the experiments, especially during the hypercapnia periods. These were sealed in airtight syringes. The actual pH, actual $p\text{CO}_2$, standard bicarbonate level and base excess were measured as proposed by Siggaard Andersen *et al* (113) and Siggaard Andersen and Engel (114) within 1 to 2 hours of sampling.

CALCULATIONS

The recorded dye dilution curves were accepted for calculations when there were no signs of marked shunts in any direction and when signs of recirculation were noted after the descending limb of the curve had fallen below 50 per cent of the maximum amplitude of the curve (60).

Signs of small right to-left or left to-right shunt flows were noted in the youngest lambs. These were ignored when it was apparent that the errors could not exceed 5 per cent.

The cardiac outputs (CO) were calculated from the Stewart-Hamilton equation

$$\text{CO} = \frac{60}{\bar{c} \cdot t} I$$

in which I is the amount of dye injected (mg), \bar{c} the mean concentration of dye (mg per liter) during the primary curve and t the duration of the primary curve in seconds. $\bar{c} \cdot t$ was obtained by measuring the area under the primary curve with a planimeter and dividing the area by a calibration factor.

The primary curve was separated from the recirculation wave in the normal way by extrapolating the declining slope on semilogarithmic paper.

The heart rate was calculated from ECG tracings which were recorded at the same time as the dye dilution curves on the same paper.

The stroke volume was obtained by dividing the cardiac output by the heart rate.

The appearance time was obtained by subtracting the catheter transit time (0.6 seconds) from the recorded appearance time.

The mean transit time (MTT) was calculated according to Hamilton (55) and Meier (86)

$$\text{MTT} = \frac{\sum c \cdot t}{\sum c}$$

The central blood volume (CBV) was calculated from

$$\text{CBV} = \text{CO} \cdot \text{MTT}$$

The relationship between the appearance time and the ratio of central blood volume to the cardiac output can be easily investigated by comparing ΔT and MTT. The assumed relationship may be expressed by

$$\Delta T = \frac{k \cdot \text{CBV}}{\text{CO}}$$

On substituting $\text{CBV} = \text{CO} \cdot \text{MTT}$ in this equation it follows that

$$\Delta T = k \cdot \text{MTT}$$

Thus a linear relationship must exist between ΔT and MTT if the initial assumption is valid.

The statistical treatment of the data was done by applying Student's t test. Regression lines were fitted to the data with an IBM 1130 computer. A difference was considered almost significant when $p < 0.05$, significant when $p < 0.01$ and highly significant when $p < 0.001$.

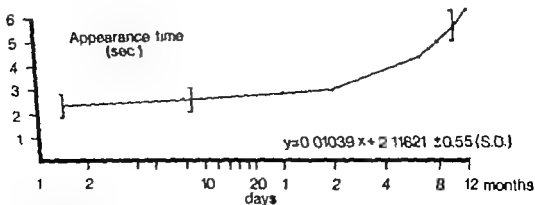
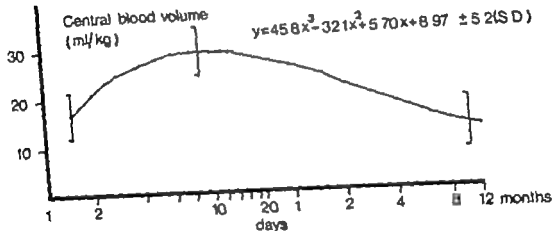
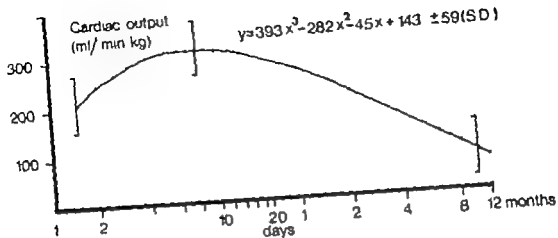


Fig. 2. Changes in cardiac output, central blood volume and appearance time with age in 45 Lurids and 9 shors. The lengths of the vertical lines are equal to $2 \times \text{S.D.}$

Results

BASAL CIRCULATORY VALUES IN NEONATAL LAMBS AND SHEEP

The circulatory parameters measured in lambs ($n=45$) and sheep ($n=9$) soon after their preparation were cardiac output heart rate stroke volume, central blood volume, the ratio of SV to CBV and the dye appearance time. The conditions that were to be fulfilled when the normal values of these quantities were measured are presented on p 18.

The mean cardiac output (Fig 3) in lambs one to two days old was about 200 ml/min kg. It increased to 300 ml/min kg at the age of 8 days ($p<0.05$) and then decreased steadily to 60 ml/min kg at the age of 12 months ($p<0.001$).

The mean central blood volume (Fig 3) varied similarly with age as the cardiac output. It increased from 16 to 28 ml/kg ($p<0.001$) from the first to the ninth day and was 12 ml/kg in sheep 12 months old ($p<0.001$).

The dye appearance time (Fig 3) increased linearly with age ($p<0.001$). Its dependence on the central blood volume and the cardiac output was studied by the mathematical methods presented in the section on methods. The relationship between appearance time (ΔT) and mean transit time (MTT) was determined for all the animals ($n=54$) up to the age of 12 months. As a linear correlation was found ΔT is directly proportional to MTT and hence to the ratio of central blood volume to cardiac output (Fig 4).

The heart rate stroke volume and the ratio SV/CBV were higher in unanesthetized lambs less than 30 days old than in sheep 11 to 12 months old (Table IV).

Effects of chloralose anesthesia on the basal values

Some of the values for unanesthetized and anesthetized lambs less than 30 days old can be compared in Table IV. Chloralose did not significantly change the cardiac output (increase 3 per cent) central blood volume (increase 8 per cent) or the dye appearance time in lambs less than 30 days old. Significant differences in heart rate stroke volume and the ratio SV/CBV were observed between the animals that were and those that were not given chloralose (Table IV). The highest recorded heart rates in anesthetized lambs were 350 and 360 per minute in two lambs.

Similar results were obtained in the animals in which the parameters were measured before and immediately after administration of chloralose (Table V).

ARTERIAL HYPOXIA IN NEONATAL LAMBS

Changes in cardiovascular function

The experimental animals used in the hypoxia studies are presented in Table III. The experiments ($n=25$) were performed under moderate hypoxia with a mean $S_{a}O_2$ of 67 ± 5.1 (SD) per cent. The changes in acid base values caused by hypoxia are presented in Tables VII and VIII. Fig 5 presents the relationship between the arterial oxygen saturation and the cardiac output in cases where both were determined simultaneously. The cardiac output increased clearly in most cases but decreases occurred as well. In some animals the output doubled. The decreases ~

TABLE V Effects of chloralose on cardiac output heart rate stroke volume central blood volume ratio SV/CBV and appearance time in veins for which data were obtained before and after administration of the drug. The number of determinations is given in parentheses in the first column.

	Before anaesthesia	10 to 15 min after chloralose administration
Cardiac output, per cent (4)	100	97 (95-100)
Heart rate beats per min (11)	1 ± 40	224 ± 47
Stroke volume, per cent (4)	100	7 (6-100)
CBV, per cent (4)	100	93 (90-100)
SV/CBV, per cent (4)	100	7 (6-100)
ΔT seconds (5)	2.0 1.5-3.0	1 (1.2-1.5)

When the B.E. was in the range from \rightarrow to -10 meq. l. (Group II, $n = 11$) the cardiac output increased from 40 to 240 ml/min/kg and then decreased below the initial level. Neither change was statistically significant.

When the B.E. was less than -10 meq. l. (Group I, $n = 4$) the output, 120 ml/min/kg

was initially lower than in the other groups ($p < 0.001$) but did not change significantly during hypoxia.

To eliminate scatter of the values caused by age and metabolic anoxia, the hypoxia data were recalculated to obtain relative changes (Fig. 7). In the calculations of the cardiac outputs, the initial relative standard deviation was taken to be 10 per cent, in initial relative S.D. of 5 per cent was assumed for the heart rate and 10 per cent for stroke volume, central blood volume and ratio SV/CBV. This treatment of the hypoxia data gave following results.

The cardiac output increased in group A by 21 to 3 per cent ($p < 0.001$). The greatest increases were almost 100 per cent, but in one case the increase was only 10 per cent. No decreases from the initial level were observed. The cardiovascular pattern of one lamb of this group is presented in Fig. 10.

In group B (B.E. \rightarrow to -10 meq. l.) the cardiac output increased significantly less than in the former group ($p < 0.001$). The mean increase of about 10 per cent in this group did not prove significant. In some

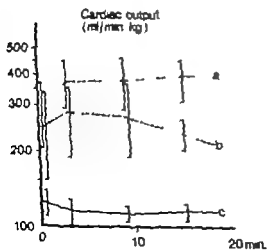


Fig. 7 Changes in cardiac output during hypoxia ml/min/kg. Vertical lines are equal to $2 \times S.D.$ in each group.

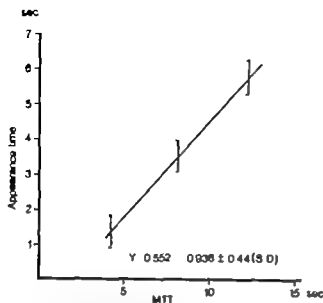


Fig. 4 Correlation between the appearance time (ΔT) and the mean transit time (MTT) in lambs and sheep ($n = 34$). The lengths of the vertical lines are twice the standard deviation.

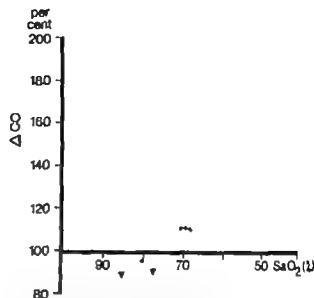


Fig. 5 Relationship between change in cardiac output and arterial oxygen saturation ($H O_2$)
 x group A (B.E. from 0 to -5 meq./L)
 • group B (B.E. from -5 to -10 meq./L)
 ▽ group C (B.E. less than -10 meq./L)

curved only in animals with metabolic acidosis (B.E. less than -5 meq./L)

The overall variation of the cardiac output in the hypoxia experiments was considerable (Fig. 6). The initial output was determined by age (Fig. 3) and the degree of metabolic acidosis (Fig. 20). Furthermore increased acidity was observed to depress the response

of cardiac output to hypoxia. For this reason, the hypoxia material was divided into three groups according to base excess (B.E.).

When the B.E. was more than -5 meq./L (Group A, $n = 10$) the mean cardiac output increased from 260 to nearly 400 ml/min/kg ($p < 0.01$) and this level was maintained throughout the hypoxia period.

TABLE IV Basal values (\pm S.D.) of heart rate, stroke volume and SV/CBV and the effect of chloralose on them. The numbers of animals are given in parentheses.

	Lambs 1.5 to 30 days old	Sheep 6 to 12 months old
Heart rate (per minute)		
No anesthesia	183 ± 50 (20)	140 ± 23 (9)
Chloralose	40 ± 43 (24)	
Difference due to anesthesia	≈ 0 per cent ($p < 0.001$)	
Stroke volume (ml/kg)		
No anesthesia	1.43 ± 0.32 (20)	0.60 ± 0.34 (9)
Chloralose	1.15 ± 0.32 (4)	
Difference due to anesthesia	1 per cent ($p < 0.001$)	
SV/CBV		
No anesthesia	0.060 ± 0.010 (20)	0.041 ± 0.008 (9)
Chloralose	0.045 ± 0.010 (4)	
Difference due to anesthesia	≈ 3 per cent ($p < 0.001$)	

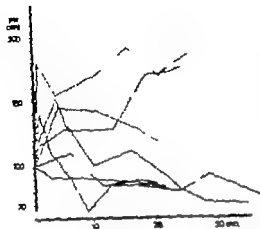


Fig. 8. Changes in cardiac output during hypoxia in lambs ventilated with respirator. Curves drawn with broken lines refer to group A ($n=3$), dot-dash lines to group B ($n=2$) and the solid line to group C ($n=1$).

animals of this group the cardiac output increased up to 1.6 times the initial value but then invariably decreased close to the starting value or below it. This kind of cardiovascular pattern is presented in Fig. 12. In one case of this group the cardiovascular pattern was one which may be considered a diving pattern (Fig. 11). In this lamb insufficient breathing was associated with bradycardia and lowered cardiac output at the beginning of the hypoxia period.

In group C (with severe metabolic acidosis (B.E. less than -10 meq/L) the cardiac output decreased progressively during hypoxia ($p < 0.05$). In one of the four animals, the cardiac output increased at first by 5 per cent but decreased immediately afterwards. The mean change in cardiac output in the group differed significantly from that in group A ($p < 0.001$) and group B ($p < 0.05$).

The cardiac output curves of the lambs ventilated with a respirator during hypoxia are presented in Fig. 8. The cardiac outputs of these lambs that were prevented from becoming hypocapnic during the hypoxia period varied generally similarly as those of lambs that hyperventilated freely and became hypo-

capnic. The cardiac output increased clearly in the lambs of group A and the high level was maintained 20 minutes or more. In the lambs of group B the outputs increased at first, but then decreased clearly. In the only experiment with a lamb of group C in which the respirator was used, a decrease in cardiac output occurred.

The effect of hypoxia on the heart rate was a slight increase in all groups in spite of the large differences in B.E. (Fig. 7). The mean increases were 6 to 13 per cent in different groups, but these were not significant. The variations of the heart rate were generally large (Table 11).

As seen in the upper part of Table 11 a high degree of metabolic acidosis did not influence the initial heart rate. The variation of the heart rate was less in severe metabolic acidosis than in normal acid-base conditions. Thus, increases of 4 to 13 per cent occurred in group C (B.P. less than -10 meq/L). In groups A and B (B.E. more than -10 meq/L) increases of 20 to 40 per cent occurred, but also considerable decreases occurred.

When the heart rate was initially high, the changes during hypoxia were small. All lambs with an initial heart rate exceeding 50 per minute were anesthetized with chloralose. When the initial heart rate varied from 100 to 50 per minute very large variations (both decreases and increases) in heart rate occurred during hypoxia in groups A and B.

The stroke volume (Fig. 7) increased by 18 to 25 per cent ($p < 0.01$) during hypoxia in group A and by about 5 per cent ($p < 0.05$) in group B. The change in the former group differed almost significantly from that in the latter group ($p < 0.05$). In group C a progressive decrease up to 19 per cent occurred ($p < 0.01$). This change differed from the change in group B ($p < 0.05$) and group A ($p < 0.001$).

The largest changes in stroke volume occurred in group A (+84 to -40 per cent).

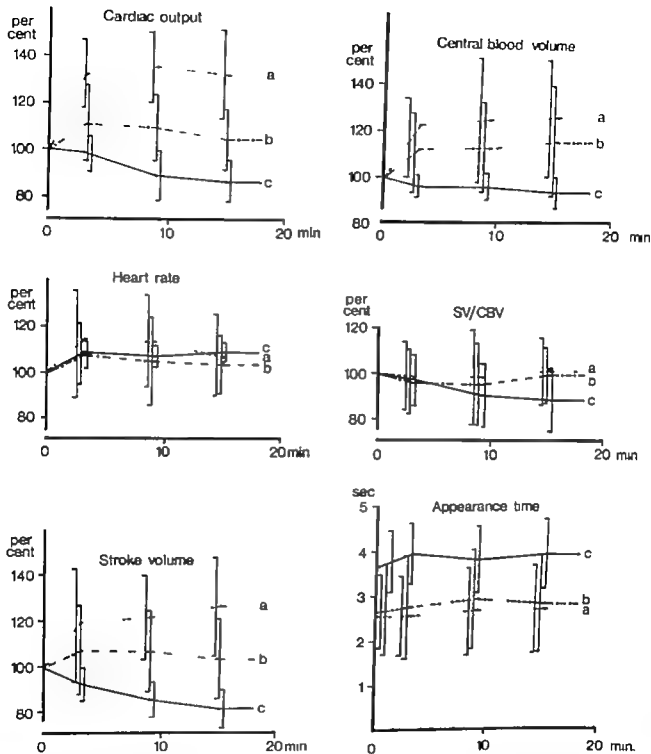


Fig 7 A ratio of cardiac output, heart rate, stroke volume, central blood volume, stroke volume/central blood volume (per cent) and appearance time (sec) during hypoxia in neonatal lambs as a function of time. Group A (BF) ($n=10$) comprised animals with B.F. < 100 mg/l; group B (BF) ($n=11$) those with B.F. from 100 to 150 mg/l; and group C (BF) ($n=4$) those with B.F. less than 100 mg/l. The vertical lines are equal to $2 \times \text{S.E.D.}$ in each group.

The ratio SA/CBV (Fig. 7) was calculated to find out whether changes in central blood volume affect the regulation of stroke volume. The mean decrease of this ratio during hypoxia was insignificant in all groups. Individual variations as large as ± 40 per cent from the initial level occurred during hypoxia. The possible significance of the ratio will be discussed later.

The dye appearance time (Fig. 7) varied greatly in the lambs during hypoxia. No significant mean changes in this parameter from the initial values occurred in groups A, B, or C. The appearance times were longer in group C than in groups A and B owing to decreased cardiac output in severe metabolic acidosis

(Bk. less than -10 meq/L). The mean appearance time in group C differed almost significantly from that in group A ($p < 0.05$).

Signs of fatal shunts were seen in the dye curves of four young lambs during hypoxia, but not constantly. A right-to-left shunt became evident when severe metabolic acidosis developed in one lamb that was excluded from the series.

Changes in acid-base balance

As mentioned before the arterial oxygen saturation varied from 44 to 86 per cent (67 ± 5.1 per cent). The lambs which were supplied with 10 per cent oxygen through a

TABLE VII Mean changes in acid-base balance during hypoxia in 17 lambs that hyperventilated freely. The ranges are given in parentheses in columns 2 and 3

	Before hypoxia	During hypoxia	Change
pH	7.33 (7.25—7.32)	7.24 (7.26—7.20)	
pCO_2 (mmHg)	37.3 (35—38)	31.8 (26—30)	-14 per cent ($p < 0.001$)
H ⁺ bicarbonate (meq/L)	20.8 (20.3—21.0)	19.1 (18.0—22.5)	-1 cent ($p < 0.001$)
D.L. (meq/L)	-1.4 (+2—-13)	-6.3 (0—-16)	

TABLE VIII Mean changes in acid-base balance during hypoxia in 4 lambs ventilated with a respirator

	Before hypoxia	During hypoxia	Change
pH	7.34 (7.29—7.43)	7.23 (7.25—7.40)	
pCO_2 (mmHg)	34 (33—35)	33 (29—39)	-6 per cent ($p > 0.05$)
H ⁺ bicarbonate (meq/L)	21 (23—19)	19.6 (20—17.5)	-11 per cent ($p < 0.01$)

TABLE VI Heart rate (beats per minute) response to hypoxia with reference to pre-experimental heart rate and degree of metabolic acidosis (groups A, B and C) The changes are differences from the initial levels.

		Number of animals	Mean initial heart rate (range)	Mean change in heart rate at 5 min. (changes during 5 min.)	Mean change in heart rate at 10 min. (changes during 10 min.)	Mean change in heart rate at 15 min. (changes during 10-15 min.)
The whole series	A	11	15 (10-310)	+10 (-40-+100)	+20 (-10-+130)	+10 (-50-+60)
	B	10	20 (10-300)	+10 (-60-+60)	+5 (-60-+80)	+10 (-60-+60)
	C	4	220 (100-660)	+10 (+10-+90)	+10 (+10-+13)	+15 (+10-+17)
Animals with an initial heart rate of 50-300/min	A	3	300 (290-310)	± 0 (-5-+10)	± 0 (-10-+5)	± 0 (-3-+10)
	B	7	260 (10-300)	+10 (-10-+20)	+10 (0-+90)	± 0 (0)
	C	1	260 (-)	+10 (+10)	+10 (+10)	+10 (+10)
Animals with an initial heart rate of 90-150/min	A		233 (130-40)	+60 (+0)	+40 (+60)	+40 (+60)
	B	4	220 (200-230)	+20 (-20-+60)	+10 (-60-+40)	+5 (-80-+70)
	C	2	215 (230-40)	+10 (+10)	+15 (+13)	+15 (+13)
Animals with an initial heart rate of 150-200/min	A	5	180 (150-190)	+60 (-40-+100)	+30 (-30-+130)	± 0 (-30-+60)
	B	1	180 (10-900)	+35 (-60-+80)	+90 (+5-+10)	+5 (-5-+30)
	C	1	160 (-)	+10 (+90)	- (-)	- (-)

Decreases were observed in three cases. In group B the greatest changes were +56 and -38 per cent decreases in stroke volume occurred at some moment during the experimental period in 9 cases out of 11. In group C the stroke volume either decreased or remained unchanged.

The changes in central blood volume (Fig 7) during hypoxia paralleled the changes in cardiac output and stroke volume. Thus, the central blood volume increased 21 to 25 per cent in group A ($p < 0.01$) and 11 to 14 per

cent ($p < 0.05$) in group B but decrease about 9 per cent ($p < 0.05$) in group C. The changes in groups A and C differed almost significantly ($p < 0.05$). The individual changes in central blood volume were about the same as those in stroke volume. Increase up to 79 per cent occurred in seven and decrease up to 13 per cent in three of the ten animals of group A. Increase up to 62 per cent occurred in six and decrease of at most 16 per cent in five of the 11 animals of group B. In group C decrease were the rule.

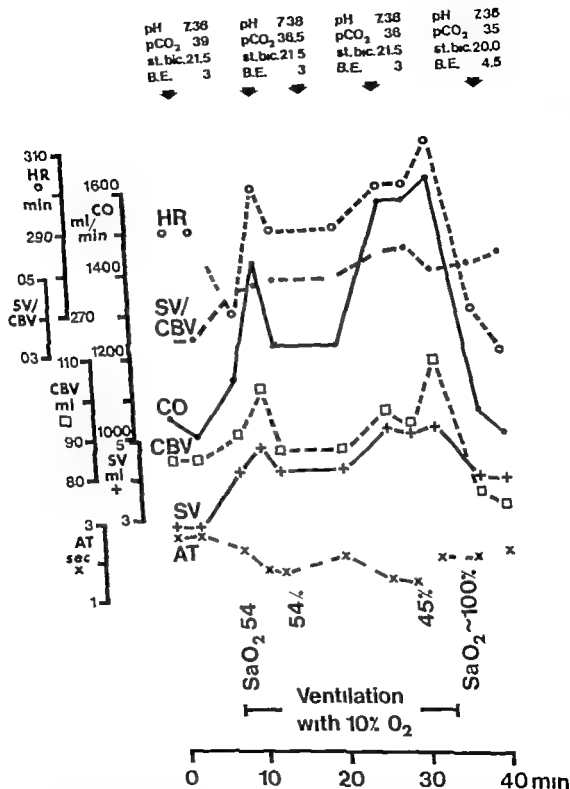


Fig. 10 The cardiovascular pattern during hypoxia in a nine-day-old lamb weighing 2.7 kg to which 200 mg of chloralose was administered and which was ventilated with a respirator. The lamb did not develop severe acidosis. During the hypoxia, CO increased clearly as a consequence of an increased SV. HB dropped at first, but increased later. The changes in AT, SV, CBV and CO are shown in the inset.

mask hyperventilated and their $p\text{CO}_2$ values decreased ($p < 0.001$) (Table VII). Owing to oxygen deficiency and elevated lactic acid concentration the standard bicarbonate level and base excess decreased significantly ($p < 0.001$). The decreases of standard bicarbonate and base excess were roughly the same in groups A, B and C. The changes in $p\text{CO}_2$ and standard bicarbonate counteracted each other so that pH of the arterial blood did not change.

Seven lambs were ventilated with a respirator during hypoxia to prevent hypocapnia. In five of these acid base values were determined both before and during the experiment (Table VIII). The decrease in $p\text{CO}_2$ was not

significant but the standard bicarbonate level decreased as it did in lambs that hyperventilated freely ($p < 0.01$).

Effect of chloralose on the cardiovascular response to hypoxia

Because a part of the lambs of the hypoxia group were anesthetized with chloralose, the results for lambs that were anesthetized and lambs that were not will be compared. The changes in cardiac output and heart rate resulting from hypoxia are shown in Fig. 9. It will be seen that the mean changes in cardiac output and heart rate during hypoxia did not differ significantly in the two groups.

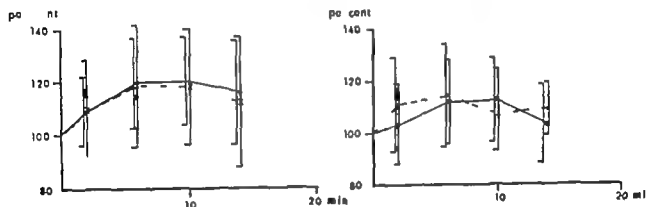


Fig. 9. Comparison of cardiac output (left) and heart rate (right) responses during hypoxia in 8 unanesthetized lambs (○) and in 10 lambs subjected to chloralose anesthesia (×). The vertical lines represent $\pm \text{S.E.}$

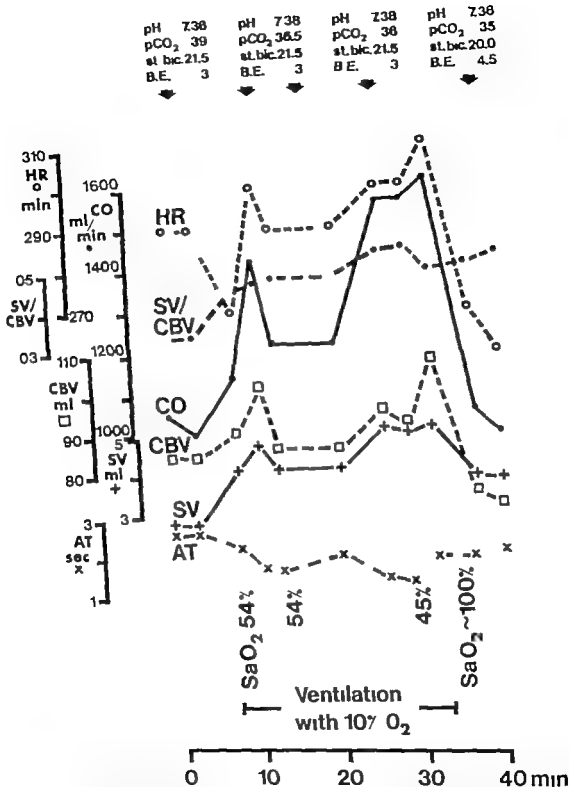


Fig. 10 The cardiorespiratory pattern during hypoxia in a nine day old lamb weighing 2.7 kg to which 200 mg of chloralose was administered and which was ventilated with respirator. The lamb did not develop severe acidosis. During the hypoxia, CO increased clearly as consequence of an increased SV. HR dropped at first, but increased later. The changes in AT, SV/CBV and CBV are not typical for the whole series. pCO₂ decreased slightly and slight decrease in BE indicated accumulation of fixed acid.

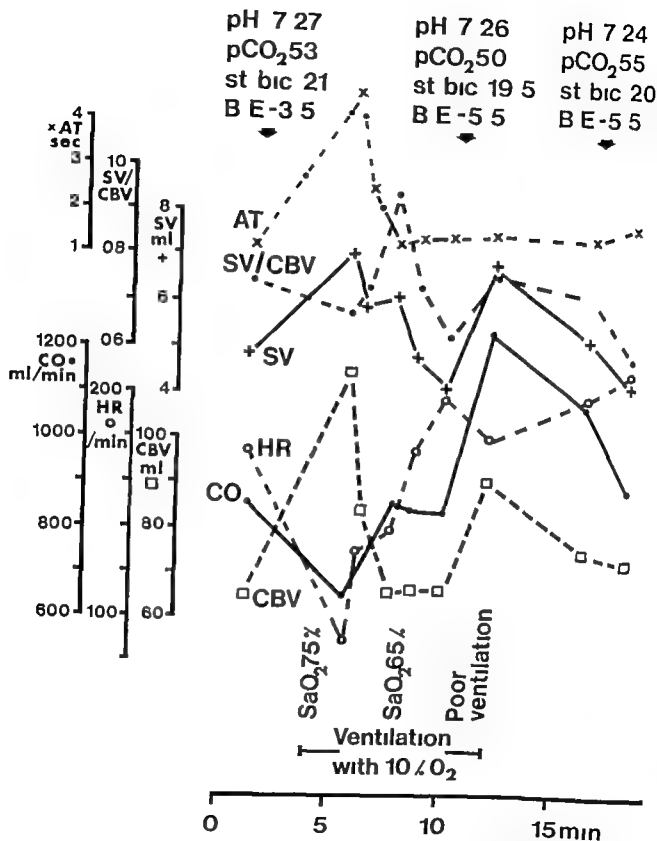


Fig. 11. The hypoxia pattern during hypoxia of a two-day-old lamb (light 70 kg) that was not anesthetized. The lamb breathed hypoxia before the hypoxia. The respiratory improved for 10 min after the induction of hypoxia. The lamb was not anesthetized. The hypoxia was induced by increased pCO₂ levels. At the beginning of the hypoxia period, the lamb developed a typical hypoxia pattern with increased CO, SV, and CBV. At the same time, CBV increased and AT decreased. The return to the initial values was observed at the end of the hypoxia period.

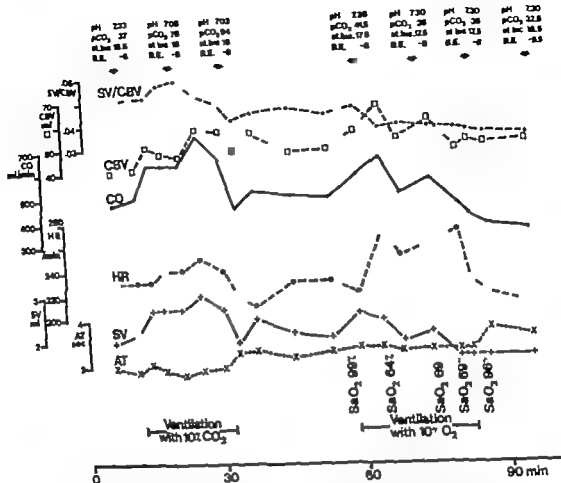


Fig. 11 A two-day-old lamb weighing 2.7 kg that, as anaesthetized with 90 mg of chloralose. Metabolic acidosis had developed before the experiment. A respirator was used although the ventilation was sufficient. Hypercapnia. On ventilation with 10 per cent CO₂, typical pattern appeared. CO increased and this was more result of increased SV than of increased HR. Also CBV increased, but AT remained practically unchanged. The values reverted to the initial levels when the supply of CO₂ was discontinued. Hypoxia. Cardiac output increased at first due to an increase in HR. Later CO fell, and change often observed in metabolic acidosis of this degree. The changes in CBV paralleled those of CO.

ARTERIAL HYPOXIA IN SHEEP

Arterial hypoxia was induced in six sheep to obtain data for comparison with the data for the lambs. In these experiments it was more difficult to induce levels of arterial oxygen saturation as low as those in the lambs. The oxygen saturation ranged from 70 to 85 per cent (mean 8 per cent) in these experiments with the sheep. Hence the results for sheep and neonatal lambs are not directly comparable.

Fig. 13 shows the changes in different circulatory parameters during hypoxia as percentages of the initial levels. In these calculations, the initial relative S.D. was taken to be 10 per cent for cardiac output stroke volume, central blood volume and the ratio SV/CBV and 5 per cent for heart rate. The mean cardiac output increased by 65 per cent ($p < 0.001$) and remained at the elevated level for at least 4 minutes. The large variation of the values of this parameter was

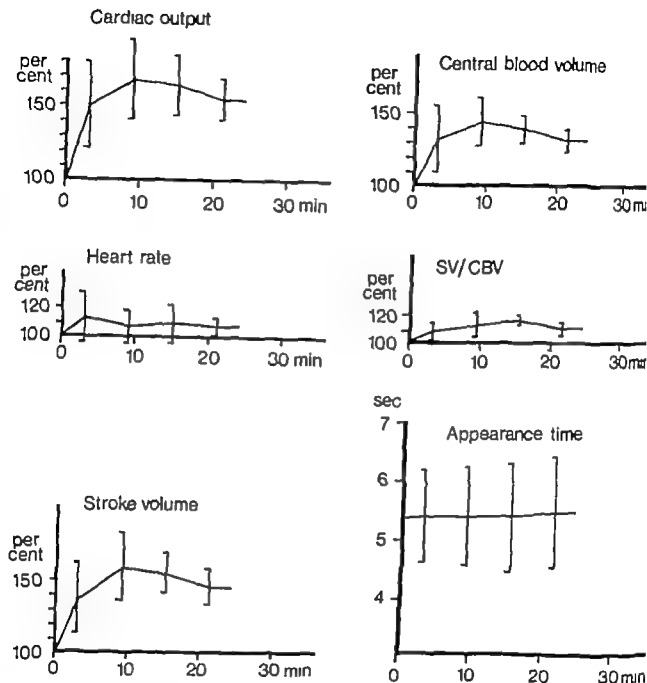


Fig 13. Changes in cardiac output, heart rate, stroke volume, central blood volume, stroke volume ratio SV/CBV (in per cent), and appearance time (in seconds) as functions of time during hypoxia in sheep from 0 to 1 mm Hg P_{O_2} . The lengths of the vertical lines are equal to $3 \times S.D.$ ($n = 6$).

probably due to differences in arterial oxygen saturation. The greatest increase, to 215 per cent of the initial level, was recorded at an arterial oxygen saturation of 75 per cent (Fig 14). The smallest increase, to 140 per cent, occurred at an arterial oxygen saturation of 82 per cent. In two experiments which lasted more than 30 minutes, the cardiac

output remained elevated throughout the hypoxia period.

The heart rate rose only 5 to 10 per cent during hypoxia ($p < 0.05$).

The changes in stroke volume were responsible for the changes in cardiac output. The mean increase in stroke volume was 56 per cent ($p < 0.001$).

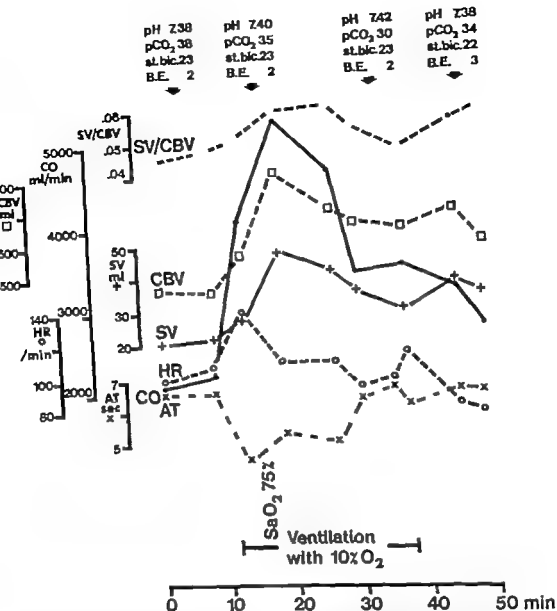


Fig. 14. Data for sheep 13 months old, eight 25 kg, under Bombardier sedation. During hypoxia with an arterial oxygen saturation of 75 per cent, CO and SV increased, but HR did not rise markedly. Also CBV increased, but despite this AT decreased. Early. Owing to hyperventilation, pCO₂ decreased.

The central blood volume changed in parallel with the cardiac output and stroke volume. It increased 4 per cent on average during the hypoxia ($p < 0.001$). The relative increase in CBV was less than the relative increase in cardiac output. Thus, a decrease in appearance time should have occurred, but

the mean appearance time did not change although the individual appearance times varied greatly. A considerable decrease in appearance time occurred in the sheep to which the case report in Fig. 14 refers.

The ratio SV/CBV did not vary as much in the sheep as in the neonatal lamb. The ratio

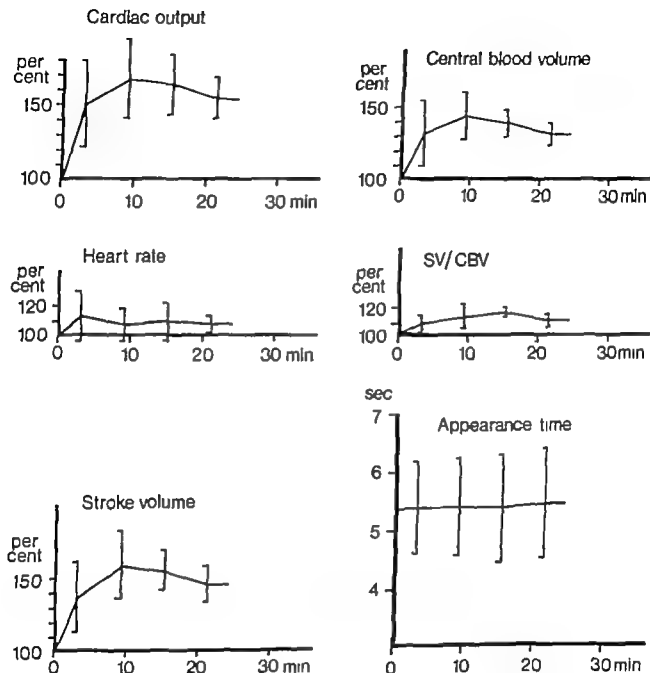


Fig 13. Changes in cardiac output, heart rate, stroke volume, central blood volume, ratio SV/CBV (in per cent) and appearance time (in seconds) as functions of time during hypoxia in sheep from 0 to 12 months old. The lengths of the vertical lines are equal to $3 \times \text{S.D.}$ ($n = 6$).

probably due to differences in arterial oxygen saturation. The greatest increase to 245 per cent of the initial level, was recorded at an arterial oxygen saturation of 75 per cent (Fig 14). The smallest increase, to 140 per cent, occurred at an arterial oxygen saturation of 82 per cent. In two experiments which lasted more than 30 minutes, the cardiac

output remained elevated throughout the hypoxia period.

The heart rate rose only 5 to 10 per cent during hypoxia ($p < 0.05$).

The changes in stroke volume were responsible for the changes in cardiac output. The mean increase in stroke volume was 56 per cent ($p < 0.001$).

TABLE IX. Acid-base values \pm S.D. of lambs before (11 determinations) and during (14 determinations) hypercapnia experiments.

	Before the experiment	During the experiment
Actual pH	7.34 ± 0.003	7.17 ± 0.005
Actual pCO_2 (mmHg)	41.9 ± 1.4	76.0 ± 18.0
St. bicarbonate (meq/L)	21.1 ± 4.2	20.7 ± 3.8

TABLE X. Heart rate changes (beats per minute) in neonatal lambs during hypercapnia.

	Number of cases	Mean initial heart rate (range)	Mean change in heart rate from initial level at 6 min. (max. variations during 0-6 min.)	Mean increase of heart rate from initial level at 1 min. (max. variations during 0-1 min.)
The whole series	14	230 (160-290)	+30 (-60-+70)	+30 (-30-+70)
Animals with initial heart rates of 250-300/min.	4	273 (240-290)	-10 (-60-+30)	± 0 (-30-+10)
Animals with initial heart rates of 200-250/min.	3	220 (200-230)	+40 (+10-+70)	+40 (0-+50)
Animals with initial heart rates of 150-200/min.	5	180 (160-190)	+30 (-20-+70)	+50 (+20-+70)

Cardiovascular changes

Different degrees of metabolic acidosis caused large differences in the initial cardiac outputs. In lambs with B.E. of 0 to -3 meq/l, the initial cardiac output ranged from 230 to 360 ml/min/kg. In a lamb with a B.E. of -11 meq/l it was 170 ml/min/kg and in another lamb with a B.E. -18 meq/l it was 80 ml/min/kg. Because of these large variations, the changes in the circulatory parameters as percentages of the initial levels were calculated assuming an initial S.D. of

10 per cent for cardiac output, stroke volume, CBV and the ratio SV/CBV and 5 per cent for heart rate.

Fig. 15 shows the circulatory changes in the lambs during hypercapnia. The cardiac output had increased 77 per cent on average ($p < 0.001$) when the experiment had lasted 10 minutes. The largest increases were up to 60 per cent of the initial level.

In two cases, initial decreases of 5 and 10 per cent occurred. Fig. 15 shows that an increase in heart rate of 13 per cent ($p < 0.001$) and an increase in stroke volume of 12 per

increased up to 12 per cent in the sheep the mean increase was significant ($p < 0.01$)

No signs of shunts were observed in the sheep

The acid base values showed a decrease of arterial pCO_2 from 42 mmHg (range 37—45 mmHg) to 35 mmHg (range 30—38 mmHg) during hypoxia. The mean change in standard bicarbonate level (from 24.5 to 24.0 meq/l) was not significant. The pH rose from a mean value of 7.39 to a mean value of 7.44 during hypoxia.

HYPERCAPNIA IN NEONATAL LAMBS

The changes in arterial acid base balance in lambs given air containing 10 per cent carbon dioxide are presented in Table IX. The arterial pCO_2 levels were normal before the experiments. In contrast the degree of metabolic acidosis varied greatly there were eight lambs with BB of 0 to —1 meq/l four lambs with BB of —1 to —10 meq/l and two lambs with BB of less than —10 meq/l

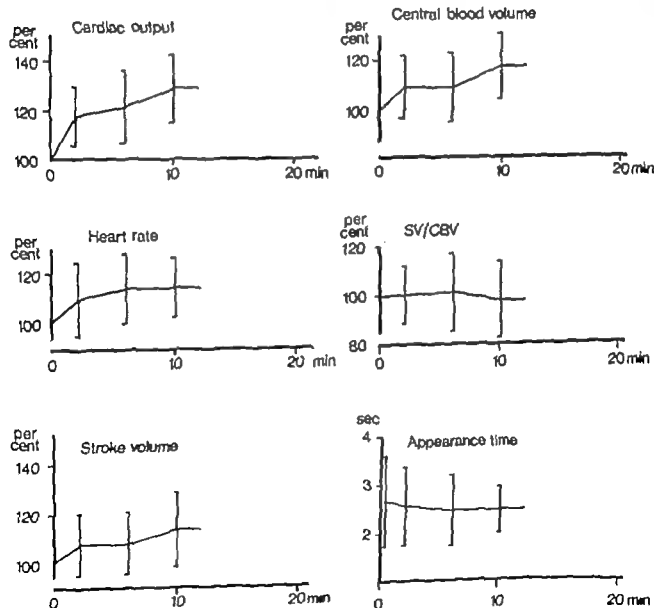


Fig. 15 Changes in cardiac output, heart rate, stroke volume, central blood volume, SV/CBV (5 per cent) and appearance time (in seconds) as functions of time in neonatal lambs during hypercapnia. The length of the vertical lines represents S.D. ($n = 14$)

TABLE IX. Acid-base values \pm S.D. of lambs before (11 determinations) and during (14 determinations) hypercapnia experiments.

	Before the experiment	During the experiment
Actual p _H	7.34 \pm 0.003	7.17 \pm 0.005
Actual pCO ₂ (mmHg)	41.0 \pm 1.4	74.0 \pm 15.0
St. bicarbonate (meq./l.)	21.1 \pm 4.	20.7 \pm 2.9

TABLE X. Heart rate changes (beats per minute) in neonatal lambs during hypercapnia.

	Number of cases	Mean initial heart rate (range)	Mean change in heart rate from initial level at 6 min. (max. variations during 0—6 min.)	Mean increase of heart rate from initial level at 15 min. (max. variations during 6—15 min.)
The whole series	14	220 (160—290)	+36 (—60—+ 6)	+20 (—20—+ 0)
Animals with initial heart rates of 250—300/min.	4	273 (260—290)	—19 (—60—+ 20)	\pm 0 (—20—+ 10)
Animals with initial heart rates of 200—250 min.	3	220 (200—230)	+46 (+10—+70)	+40 (0—+ 80)
Animals with initial heart rates of 150—200 min.	7	180 (160—190)	+40 (—20—+ 70)	+50 (+20—+70)

Cardiovascular changes

Diff. rent degrees of metabolic acidosis caused large differences in the initial cardiac outputs. In lambs with B.E. of 0 to —5 meq/l., the initial cardiac output ranged from 230 to 360 ml/min/kg in a lamb with a B.E. of —11 meq/l. it was 120 ml/min/kg and in another lamb with a B.E. —18 meq./L. it was 80 ml/min/kg. Because of these large variations, the changes in the circulatory parameters as percentages of the initial levels were calculated assuming an initial S.D. of

10 per cent for cardiac output, stroke volume, CBV and the ratio SV/CBV and 5 per cent for heart rate.

Fig. 15 shows the circulatory changes in the lambs during hypercapnia. The cardiac output had increased 97 per cent on average ($p < 0.001$) when the experiment had lasted 10 minutes. The largest increases were up to 60 per cent of the initial level.

In two cases, initial decreases of 5 and 10 per cent occurred. Fig. 15 shows that an increase in heart rate of 13 per cent ($p < 0.001$) and an increase in stroke volume of 1 per

cent ($p < 0.01$) had the same effect on the cardiac output response.

The initial heart rate seemed to determine its response during hypercapnia (Table A). When the initial heart rate was high (> 250 /min) the rate increased only slightly to a maximum value of 300 per minute in two animals, and decreased in two animals. When the initial heart rate was from 150 to 250 per minute, an increase usually occurred.

The stroke volume increased 12 per cent on average during 10 minutes of hypercapnia ($p < 0.01$). Large variations occurred; the largest increase was 50 per cent and in three cases the stroke volume decreased 5 to 25 per cent.

The central blood volume changed in parallel with the stroke volume. The mean increase in central blood volume at the tenth minute of the experiment was 16 per cent ($p < 0.001$).

As could be expected from the parallel variations of SV and CBV the mean ratio SV/CBV did not change at all. Individual variations up to ± 35 per cent occurred in this parameter.

The dye appearance time also varied considerably in different animals during hypercapnia; both increases and decreases were observed, but the mean change was an insignificant decrease.

There were signs of small right to-left shunts in the dye dilution curves of the lambs during hypercapnia. The curves for one lamb (see Fig 17) exhibited a large right to-left shunt during the hypercapnia period.

Fig. 12 shows a typical cardiovascular pattern during hypercapnia for a lamb with moderate metabolic acidosis. Among the animals there were two interesting cases. Fig 17 shows a total A-V block which developed during hypercapnia in a lamb with severe metabolic acidosis. The heart rhythm reverted to normal when the supply of air containing 10 per cent carbon dioxide was replaced with air. Fig 18 presents a case with a probable sinus bradycardia and its response to hypercapnia.

Effects of chloralose anesthesia

As mentioned before metabolic acidosis developed generally more rapidly in lambs subjected to chloralose anesthesia than in unanesthetized lambs. Chloralose was administered to eight lambs of the hypercapnia series. The two lambs with BE of less than -10 meq/l were anesthetized. Chloralose seems to depress the cardiac output and heart rate responses ($p < 0.05$) during hypercapnia (Fig 18).

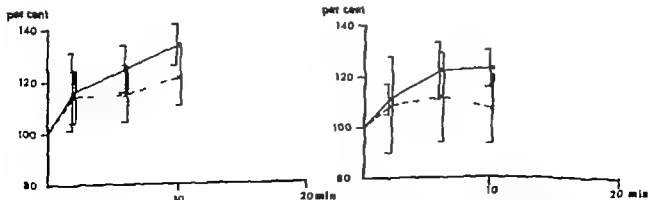


Fig 18 Mean changes in cardiac output (left) and heart rate (right) during hypercapnia in six unanesthetized lambs (O) and eight lambs subjected to chloralose anesthesia (X). The lengths of the vertical lines are equal to $\times 8 D$.

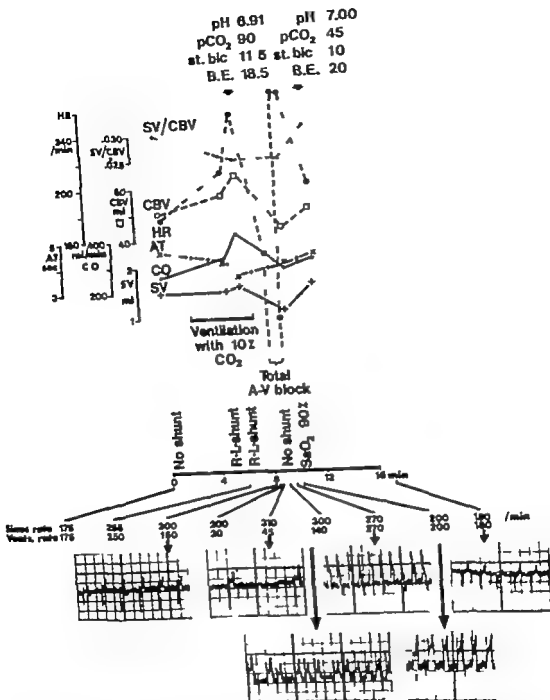


Fig 17 Total A-V block in lamb 40 hours old, weight 1.3 kg, under chloralose anesthesia. The lamb was not anesthetized at first but as it was observed to shiver, 160 mg of chloralose was administered. As this caused respiratory arrest, ventilation with respirator was begun. As result of inadequate ventilation, combined respiratory and metabolic acidosis developed. During hypercapnia experiment, HR and probably CO increased. After 5 minutes, the ventricular rate suddenly slowed down to 30 beats per minute but the ventricular rate continued to be 300 beats per minute. At that time ventilation with 10 per cent CO₂ was discontinued and extracorporeal heart massage was performed for few seconds, after which an immediate improvement was seen in the ECG. I up of the normalized heart rate, ST T changes suggesting myocardial damage were seen. The ECG reverted to the initial normal pattern when some minutes had elapsed after the block.

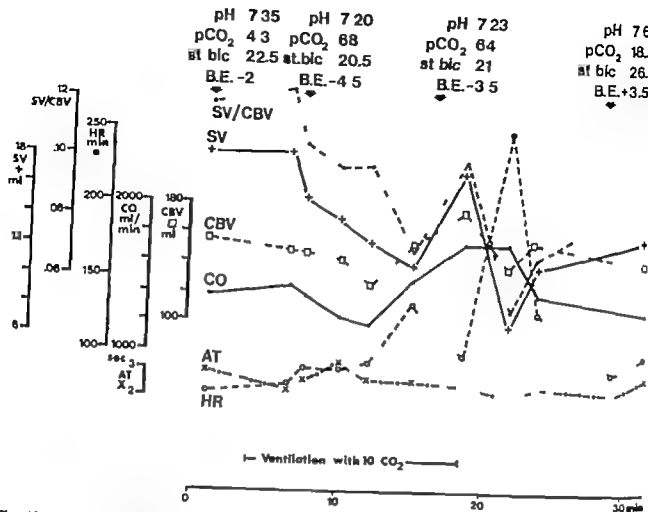


Fig 18. A 14-day-old lamb, weighing 4. kg, not anesthetized. When preparation was begun, the HR of the lamb was abnormally low (from 70 to 90 per minute). Judging from FCG records this rhythm arose from the sinus node but because of the poor quality of the ECG the possibility of a total A-V block could not be excluded. During the hypercapnia period, the cardio-vascular pattern was completely atypical. At the 15th to 14th minute of the experiment CO increased slightly. However, after the experimental period when the lamb was breathing air a pronounced tachycardia developed and remained at the high level seen in late hypercapnia. This period of tachycardia ceased within 30 seconds and the earlier low HR returned. During these changes the form of the QRS complex remained essentially unchanged, indicating a regular or at least nodal pacing of the heart.

HYPERCAPNIA IN SHEEP

Hypercapnia was induced in two sheep 12 months old. In both sheep the acid base values were almost normal before the experiment (pH 7.39 and 7.41 pCO₂ 37 and 39 mmHg standard bicarbonate 23 and 24 meq/L and BE -2 and -3 meq/L). During hypercapnia, the actual pCO₂ values increased to 74 and 82 mmHg and the pH values decreased to 7.1 and 7.18 respectively in the two sheep.

The cardiovascular changes observed in these sheep are presented in Fig 19. The

changes in cardiac output stroke volume and central blood volume resemble those observed in the neonatal lambs. The heart rate decreased in one sheep and remained unchanged in the other.

METABOLIC ACIDOSIS IN NEONATAL LAMBS

The cause of the metabolic acidosis observed in many lambs during this study is somewhat problematic. In some animals it clearly de-

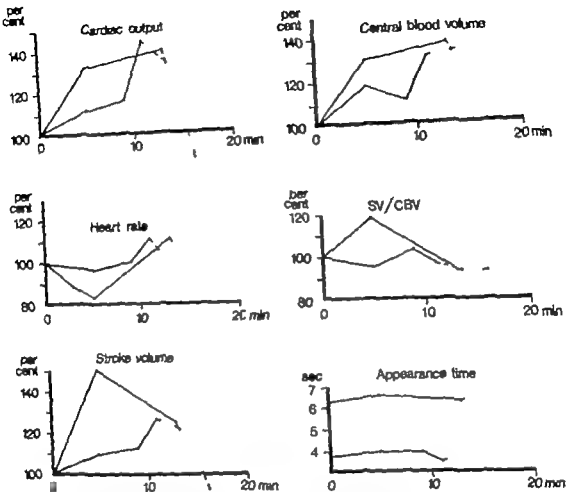


Fig 12. Changes in cardiac output, heart rate, stroke volume, central blood volume, ratio SV/CBV (in per cent) and appearance time (in seconds) in two 12-month old sheep during hypercapnia. The solid lines refer to the experimental period and the broken lines to the air-breathing period.

developed during experimental hypoxia (Tables VII and VIII) but it seemed to develop spontaneously in many animals. The lambs with metabolic acidosis were younger on average than the other lambs (Table III). The lambs were often distressed when placed on the table: they breathed quickly, shivered and were restless. Administration of chloralose clearly favored the development of metabolic acidosis. Eight of the nine neonatal lambs were anesthetized with chloralose. After its administration, the lambs often began to breathe rapidly and shallowly but no clear

signs of arterial hypoxia were detected. There were also other lambs in which metabolic acidosis developed, but only in these nine animals were the cardiovascular parameters and acid-base values measured simultaneously. Only lambs with $p\text{CO}_2$ of less than 45 mmHg were accepted for this analysis.

The progressive variation of the acid-base values in the nine lambs is presented in Table XI. The values are grouped into initial normal values (9 determinations), values when the B.E. was from -6 to -1 (9 determinations) and values when the B.E. was from -1 to

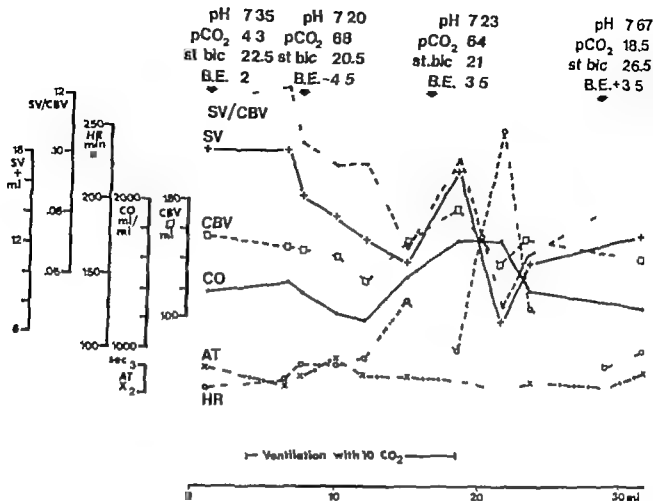


Fig 18. A 14-day-old lamb, weighing 4 kg, not anesthetized. When preparation was begun, the HR of the lamb was abnormally low (from 70 to 90 pc/minute). Judging from ECG records, this rhythm arose from the sinus node but because of the poor quality of the ECG the possibility of total A-V block could not be excluded. During the hypercapnia period the cardio-vascular pattern was completely typical. At the 15th to 18th min to of the experiment CO increased slightly. However after the experimental period when the lamb was breathing air a pronounced tachycardia developed and remained at the high level seen in late hypercapnia. This period of tachycardia ceased within 30 seconds and the earlier low HR returned. During these changes the form of the QRS complexes remained essentially unchanged, indicating auricular or at least nodal pacing of the heart.

HYPERCAPNIA IN SHEEP

Hypercapnia was induced in two sheep 12 months old. In both sheep the acid base values were almost normal before the experiment (pH 7.39 and 7.41, pO₂ 37 and 39 mmHg, standard bicarbonate 23 and 24 meq/l and B.E. -2 and -3 meq/l). During hypercapnia the actual pO₂ values increased to 74 and 82 mmHg and the pH values decreased to 7.21 and 7.18 respectively in the two sheep.

The cardiovascular changes observed in these sheep are presented in Fig 19. The

changes in cardiac output, stroke volume and central blood volume resemble those observed in the neonatal lambs. The heart rate decreased in one sheep and remained unchanged in the other.

METABOLIC ACIDOSIS IN NEONATAL LAMBS

The cause of the metabolic acidosis observed in many lambs during this study is somewhat problematic. In some animals it clearly de-

TABLE XL Acid-base values (means and ranges) in lambs with developing metabolic acidosis. The numbers of determinations are given in parentheses in the captions.

	Initial values (9)	Lambs with B.E. of -6 to -12 (9)	Lambs with B.E. of -12 to -20 (3)
Arterial pH	7.37 (7.33-7.43)	7.31 (7.29-7.36)	7.14 (6.9-7.21)
Arterial pCO ₂ (mmHg)	41 (38-45)	34 (30-38)	36 (26-43)
St. bicarbonate (meq/L)	33.1 (23-34)	17.1 (15-19.5)	13.0 (10-16)
B.E. (meq/L)	-1 (0--2.5)	-9 (-6--12)	-16 (-13--20)

almost entirely by the decrease in stroke volume

The changes in central blood volume were not so marked as those in the above parameters. It decreased by 18 per cent when the B.E. decreased by 10 meq/L ($p < 0.01$). In two lambs an increase occurred. The ratio SV/CBV was found to decrease by 23 per cent for a decrease of 10 meq/L in B.E. ($p < 0.001$). As may be expected from the relatively small decrease in CBV in comparison with that in cardiac output, the dye

appearance time increased clearly as metabolic acidosis developed. The increase was 1.2 seconds for a decrease of 10 meq/L in B.E. ($p < 0.001$).

No signs of fetal shunts were present in dye dilution curves of the lambs of this series. It was, however, impossible to decide with certainty whether a left-to-right shunt was present or not. This difficulty was due to the slow descent of the dye dilution curve when the cardiac output was low.

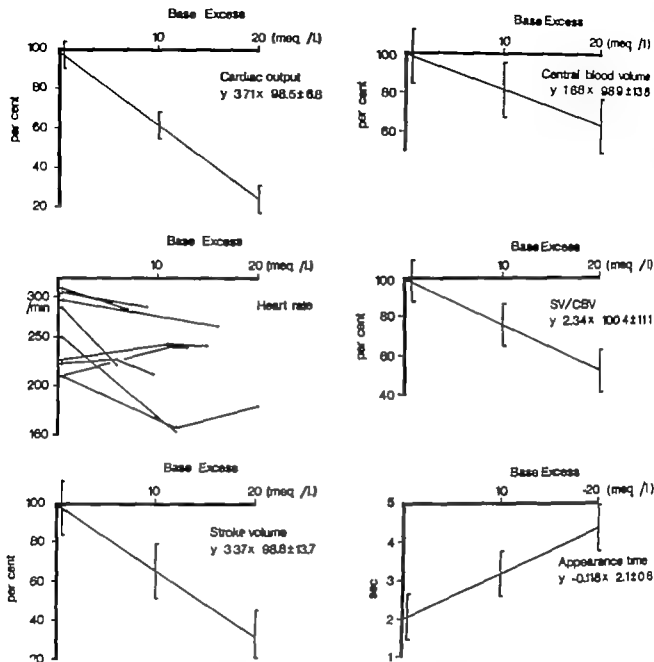


Fig 20 Cardiac output heart rate stroke volume, central blood volume ratio SV/CBV and appearance time as functions of base excess ($n=9$). The lengths of the vertical lines are equal to $\times 8.7$.

—20 meq/l (5 determinations). With decreasing standard bicarbonate, the pH decrease seems to have been compensated for initially by a decrease in arterial pCO_2 . As the metabolic acidosis progressed the pCO_2 no longer decreased and the net effect was a lowered pH.

Fig 20 presents the changes in the circulatory parameters in relation to the B.E.

The cardiac output decreased by 39 per cent for a decrease of 10 meq/l in B.E. ($p < 0.001$). The heart rate showed a more variable pattern. In most cases it decreased but in three cases it remained unchanged or increased. The stroke volume definitely decreased the decrease being 30 per cent for a decrease of 10 meq/l in B.E. ($p < 0.001$). The decrease in cardiac output was caused

TABLE XI. Acid-base values (means and ranges) in lambs with developing metabolic acidosis. The numbers of determinations are given in parentheses in the captions.

	Initial alocs (9)	Lambs with B.E. of -6 to -12 (9)	Lambs with B.E. f -12 to -20 (5)
Actual pH	7.37 (7.25-7.45)	7.31 (7.29-7.36)	7.14 (6.9-7.31)
Actual pCO ₂ (mmHg)	41 (33-45)	34 (30-35)	34 (30-45)
Ser. bicarbonate (meq./l.)	22.1 (23-24)	17.1 (15-19.5)	12.0 (10-14)
B.E. (meq./l.)	-1 (0--2.5)	-9 (-6--12)	-16 (-12--20)

almost entirely by the decrease in stroke volume.

The changes in central blood volume were not so marked as those in the above parameters. It decreased by 18 per cent when the B.E. decreased by 10 meq./l. ($p < 0.01$). In two lambs an increase occurred. The ratio SV/CBV was found to decrease by 23 per cent for a decrease of 10 meq./l. in B.E. ($p < 0.001$). As may be expected from the relatively small decrease in CBV in comparison with that in cardiac output, the dye

appearance time increased clearly as metabolic acidosis developed. The increase was 1.2 seconds for a decrease of 10 meq./l. in B.E. ($p < 0.001$).

No signs of fetal shunts were present in dye dilution curves of the lambs of this series. It was, however, impossible to decide with certainty whether a left-to-right shunt was present or not. This difficulty was due to the slow descent of the dye dilution curve when the cardiac output was low.

Discussion

METHODS

Chloralose anesthesia

Anesthesia in experimental animals is always a compromise and is used when one wishes to avoid larger disturbances than the anesthetic causes. The decision to use it or not depends on what functions of the circulation are to be studied and how much anesthesia affects these functions.

Korner (73) stressed the importance of not using anesthesia in studies of the effects of experimental hypoxia in rabbits because of the large variations in circulatory response caused by anesthesia. On the other hand, avoidance of anesthesia may have the disadvantage that anxiety reactions arise during distressing conditions. It has been shown that anxiety may increase the cardiac output by 35 per cent (54).

Chloralose was used as anesthetic in the present study in the doses recommended by Cross *et al.* (26). Massive pulmonary edema occurred once and sudden death occurred twice in lambs anesthetized with these doses. For this reason, chloralose was administered in the latter part of the study only to lambs that were observed to shiver and when tracheotomy was considered necessary.

In general, the chloralose administration promoted the development of metabolic acidosis and caused tachycardia. It may also have had a depressing effect on the cardiac response to hypercapnia (Fig. 16) but no effect on the cardiac response to hypoxia was found.

The unanesthetized lambs remained surprisingly calm during the hypoxia and hypercapnia experiments. Only increased respiratory effort was observed constantly but the animals were not usually restless. The anesthesia hence appears not to be necessary in experiments of the type performed on neonatal lambs in the present study if procedures like tracheotomy do not require it.

Preparation and experiments

The procedures requiring surgery were done so as to be as little traumatic as possible. According to Korner (73) catheterization of major vessels should be avoided in hypoxia experiments. The femoral artery and superficial jugular vein were the only vessels catheterized in this study. These procedures hardly influenced the circulation significantly.

The warming plate on which the lambs were laid appeared to be necessary. If it was not used, the body temperatures of the lambs tended to fall. When it was used the animals maintained a normal temperature of 39 to 41°C.

The total blood volume of about 15 ml removed during the experiments was at most 9 per cent of the assumed total blood volume in the smallest lambs. The blood losses were replaced with saline or in some cases, with blood from the ewe. No blood incompatibility was observed between the lambs and their own ewes in a simple cross-matching test.

During experiments lasting 3 to 4 hours,

an actual blood loss was still a possibility. This may have influenced the results concerning the effects of metabolic acidosis on the circulation of neonatal lambs.

Measurements

At present the dye dilution method seems to be the method of choice for circulatory studies in newborn infants and lambs, because of its small disturbing effects on the cardiovascular functions. The Fick principle is not applicable in experiments in which a steady state may not be obtained (43, 78, 88, 69, 134). Flow meters which permit simultaneous measurements of flow through different vessels mostly require thoracotomy which causes cardiac shrinkage (106). The pulse-contour method which measures every stroke volume separately is not yet accurate enough, but probably will be useful for flow measurements in the future (130).

The blood withdrawn through the cannula was from 10 to 15 ml in the experiments with the lambs. If the lamb is assumed to have a blood volume of 80 ml/kg, the removed blood volume, which was returned, was 9 per cent of the total blood volume of the smallest lamb (1 kg). A blood loss of this magnitude has been found by Wallgren *et al.* (127) to decrease cardiac output and stroke volume and to increase the peripheral resistance in newborn infants. Therefore, low values of these parameters may have been recorded for the smallest lambs.

The fetal shunts which occurred in the youngest lambs were somewhat disturbing as they made calculations from dye curves difficult. Therefore lambs younger than 36 hours were not used. In older lambs signs of shunts were sometimes observed but not constantly. Curves which indicated large shunts were rejected. The shunt flows were not calculated because the study was mainly concerned with cardiac function.

The self-designed dye-dilution apparatus was found to yield results of satisfactory accuracy (Figs. 1 and 2). The test results for the artificial flow system were good, but the accuracy was not as good in the experiments with lambs owing to less accurate calibration when blood than when water was the liquid. As concluded from successive measurements of cardiac output in steady state conditions, the maximum errors were up to ± 15 per cent. Mostly successive determinations agreed within ± 10 per cent. The accuracy of this apparatus seems thus to be equal to that of commercial apparatus. A disadvantage of the apparatus was that it required constant watching; therefore, other valuable measurements, such as those of arterial and other pressures, could not be done concurrently.

Temperature measurement with a rectal electrode is not so accurate as with an esophageal electrode because the former electrode follows the temperature of body core more slowly than the esophageal electrode. The use of an esophageal electrode in unanesthetized lambs was unsuccessful because the lambs became restless and vomited easily. In the experiments with lambs the temperature range was narrow as no quick changes occurred owing to the warming plate. Therefore the measurement of rectal temperature may be considered to have been satisfactory.

The micro method developed by Siggaard Andersen *et al.* (113) and Siggaard Andersen and Engel (114) for measuring acid-base values is in common clinical use and was therefore applied in this study. The measurement of standard bicarbonate makes it possible to obtain direct data on the content of fixed acids without any influence of the partial pressure of carbon dioxide. The standard deviations of the method given by the authors are 0.006 units for pH, per cent for $p\text{CO}_2$, and 0.3 meq./l. for standard bicarbonate when the values are in the normal ranges (113).

Discussion

METHODS

Chloralose anesthesia

Anesthesia in experimental animals is always a compromise and is used when one wishes to avoid larger disturbances than the anesthetic causes. The decision to use it or not depends on what functions of the circulation are to be studied and how much anesthesia affects these functions.

Korner (73) stressed the importance of not using anesthesia in studies of the effects of experimental hypoxia in rabbits because of the large variations in circulatory response caused by anesthesia. On the other hand, avoidance of anesthesia may have the disadvantage that anxiety reactions arise during distressing conditions. It has been shown that anxiety may increase the cardiac output by 35 per cent (54).

Chloralose was used as anesthetic in the present study in the doses recommended by Cross *et al* (26). Massive pulmonary edema occurred once and sudden death occurred twice in lambs anesthetized with these doses. For this reason chloralose was administered in the latter part of the study only to lambs that were observed to shiver and when tracheotomy was considered necessary.

In general the chloralose administration promoted the development of metabolic acidosis and caused tachycardia. It may also have had a depressing effect on the cardiac response to hypercapnia (Fig 16) but no effect on the cardiac response to hypoxia was found.

The unanesthetized lambs remained surprisingly calm during the hypoxia and hypercapnia experiments. Only increased respiratory effort was observed constantly but the animals were not usually restless. The anesthesia hence appears not to be necessary in experiments of the type performed on neonatal lambs in the present study if procedures like tracheotomy do not require it.

Preparation and experiments

The procedures requiring surgery were done so as to be as little traumatic as possible. According to Korner (73) catheterization of major vessels should be avoided in hypoxia experiments. The femoral artery and superficial jugular vein were the only vessels catheterized in this study. These procedures hardly influenced the circulation significantly.

The warming plate on which the lambs were laid appeared to be necessary. If it was not used the body temperatures of the lambs tended to fall. When it was used, the animals maintained a normal temperature of 30 to 41°C.

The total blood volume of about 15 ml removed during the experiments was at most 9 per cent of the assumed total blood volume in the smallest lambs. The blood losses were replaced with saline or in some cases, with blood from the ewe. No blood incompatibility was observed between the lambs and their own ewes in a simple cross-matching test.

During experiments lasting 3 to 4 hours,

11 thinks are lacking in the literature. As a
12 result of the increased heart rate a decrease
13 in stroke volume, and consequently also in
14 the ratio SV/CBV occurred in the anesthe-
15 tized lambs. The cardiac output and CBV
16 were not significantly influenced by the
17 drug. This agrees with the results of Wiggers
18 (13) who found no change in the cardiac
19 output of adult dogs after administration of
20 chloralose.

The present data do not allow one to draw any conclusions about fetal shunts, because animals with large shunts were rejected. In normal steady state conditions, the lambs more than 36 hours old rarely showed signs of shunts, but patent arterial ducts were observed at autopsy in lambs without any signs of shunts in the dye curves.

EFFECTS OF ARTERIAL HYPOXIA

When the literature on hypoxia ten to forty years old is reviewed, greatly varying results and statements are found. This variability appears to have been due to differences in experimental methods, conditions and animals.

The results obtained in this study differ somewhat from the results of earlier studies on neonatal lambs. Cross *et al.* (26) and Stahlman *et al.* (117) did not find any significant change in cardiac output in neonatal lambs during hypoxia whereas a significant increase in cardiac output was observed in this study when the acid-base conditions were normal. Cross *et al.* applied the Fick principle; this may have led to the measurement of unchanged cardiac outputs as discussed in the section on methods. Metabolic acidosis may have developed in the lambs due to progressive hypoxia during the long experimental periods they employed. Complete data on the acid-base balances were not given, but lactic acid concentrations up to 82 mg per 100 ml were reported. This corresponds to

almost 10 mcg/l., and according to the present results, the cardiac output does not increase during hypoxia when this degree of metabolic acidosis prevails. The difference between the present results and those of Stahlman *et al.* (117) cannot be explained, because the only pronounced difference was that they used eight per cent oxygen and 10 per cent oxygen was supplied to the lambs in this study.

The change in cardiac output was poorly correlated with the arterial oxygen saturation level when seldom was disregarded (Fig. 5). According to Korner (73) the increase in cardiac output is correlated with the degree of hypoxia in insura. As evidence for this statement, he presented data of different authors which showed that the increase in cardiac output correlates very well with oxygen saturation in mixed venous blood (73). Surprisingly the same correlation was found in man, rabbit and dog.

Although an increase of cardiac output occurred in the lambs during hypoxia when acid-base conditions were normal, the increase was clearly smaller in lambs than in sheep. The cardiac output increased by 31 to 36 per cent in lambs with a mean arterial oxygen saturation of 67 per cent (Fig. 7) whereas the increase was 55 per cent in sheep with a mean arterial oxygen saturation of 76 per cent (Fig. 13). An explanation for the weak response of the heart in newborn during hypoxia may be that the heart is simply working at almost full capacity and is therefore unable to increase its output as much as the adult heart.

is mentioned in the literature review neurohumoral regulation is not essential for increased cardiac function during hypoxia in adults. Hence the reason for the weak response of the cardiac output of lambda to hypoxia must be found in the heart itself. It is known that the myocardial enzyme pattern of newborn rats is such that energy production by anaerobic glycolysis is capable of maintaining heart function in anoxia.

BASAL CIRCULATORY VALUES

Measurement of basal conditions in the circulation seems to require normal acid-base values. A decrease of 1 meq/l in B.E. was found to decrease the cardiac output by about four per cent and increased levels of carbon dioxide were found to increase the cardiac output. Therefore, the required normal limits of B.E. were ± 3 meq/l and those for $p\text{CO}_2$, 40 ± 5 mmHg.

It was observed that the cardiac output (ml/min/kg) increased by 50 per cent during the first eight days of life and decreased subsequently to adulthood. The cardiac outputs of lambs less than 30 days old were smaller than those reported by Cross *et al.* (26) and even smaller than those reported by Stahlman *et al.* (117). The cardiac output values for the youngest lambs agree well with those observed by Mahon *et al.* (84) for full term fetal lambs and by Assali *et al.* (9) for newborn lambs. As mentioned before the dye dilution method may have given cardiac output values approximately 10 per cent too low for the youngest lambs.

The increase in cardiac output during the first eight days of life appears reasonable because the oxygen consumption per kilogram increases and the oxygen-carrying capacity of the blood decreases during this period (26). The variation of cardiac output in newborn infants during this period has not been measured. It would be expected to increase during the first two weeks of life because the oxygen consumptions of normal and premature infants increase clearly during this period (79-109). Also the decrease in circulation time in newborn infants during the first three weeks after birth that was observed by Jegier *et al.* (66) may indicate an increasing cardiac output.

The central blood volume has not previously been measured in neonatal lambs. It changed in parallel with the cardiac output. This relationship has been observed also in human

adults in which it is maintained during exercise (115). This relationship is not a methodological characteristic of the dye dilution method, because the area below the primary curve from which the cardiac output is determined and the mean transit time change independently. The CBV was a maximum 28 ml/kg at the age of nine days. If the total blood volume were 80 ml/kg the CBV would amount to 35 per cent of the total blood volume. This is close to the value 38 per cent reported for human adults by Heggin *et al.* (60).

The ratio of OBV to the total blood volume in sheep 12 months old is only 16 per cent if the total blood volume is 80 ml/kg; this percentage is much lower than that observed in adult humans (60).

The distribution of blood apparently changes immediately after birth so that blood is shifted from the peripheral circulation to the intrathoracic space. Subsequently there occurs a shift in the opposite direction. The decrease in the ratio SV/CBV to adult hood possibly indicates that the blood distribution changes within the central circulation so that the blood in the heart is a smaller proportion of the CBV and consequently the SV becomes smaller in comparison with CBV. The large hearts of newborn infants relative to body size agree with these conclusions.

The appearance time did not decrease in lambs after birth as it does in infants (66) but increased linearly with age. It was found that the AT is directly proportional to the ratio of CBV to cardiac output. This is in agreement with the earlier observation that a change in the site of injection in a peripheral or central vein does not alter the circulation time significantly (66).

Chloralose anaesthesia was found to cause tachycardia in lambs. The same has been observed in adult dogs (60). The reason for this may be either a sympathomimetic action or inhibition of the vagus nerve by chloralose. Arguments supporting one of these possi-

agree with earlier findings for dogs (11, 61, 67, 89, 107, 120). Marshall and Shephard (85) claimed that the increased CBV is distributed over the large arteries during exercise. This cannot occur in lambs during hypoxia, because the mean arterial pressure decreases (117). Further aortographies made in our laboratory reveal that the caliber of the aorta remains unchanged or decreases slightly during hypoxia. Thus, the most probable space available for the increased CBV is the pulmonary vascular bed and the heart. This conclusion is not, however, in agreement with the finding of Stahlman *et al.* (117) that the pulmonary blood volume measured by the slope method and the volume calculated from pulmonary transit time decrease during hypoxia in newborn lambs.

The ratio SV/CBV was calculated to determine whether the stroke volume is determined by the central blood volume. This ratio is free from errors in the calibration of the dye dilution apparatus. It may be calculated also as $1/HR \cdot MTT$ and both the heart rate and the mean transit time can be measured more accurately than SV or CBV . Therefore it was surprising that there occurred large individual variations in this ratio during hypoxia, although the mean changes in the different groups of lambs were insignificant.

In contrast to lambs, the ratio SV/CBV increased by more than 10 per cent ($p < 0.01$) in sheep. This difference may be ascribed to improved ventricular function during hypoxia in the sheep which makes an increased stroke volume possible without increased CBV and left ventricular end-diastolic pressure. Unfortunately the left atrial pressures were not measured.

As presented in the literature review the diving pattern has been found to occur in many mammals in certain circumstances. Elmer *et al.* (40) observed it in calves 10 days after birth. The responses to hypoxia of fetal lambs at term described by Aswell *et al.* (18) resemble the diving pattern, i.e. brady-

cardia, increased carotid and umbilical flows and decreased femoral flow were observed.

The hypoxia experiment on a lamb days old presented in Fig. 11 revealed signs of a diving pattern, i.e. bradycardia and decreased cardiac output. The diving pattern is considered to occur in a seal when it cannot breathe (108) and in a rabbit during hypoxia because its respiratory response to hypoxia is poor (74). The lamb presented here breathed poorly and this caused its arterial pCO_2 to increase above normal. Increased pCO_2 was hardly responsible for the depressed cardiac function, because combined hypoxia and hypercapnia result in increased cardiac outputs (unpublished data).

The development of the diving pattern in newborn mammals remains to be investigated more closely. If it is found to occur repeatedly in newborn lambs and infants, it indicates a strong vasomotor control by the central nervous system and would be clinically important.

EFFECTS OF HYPERCAPNIA

Hypercapnia is known to increase the cardiac outputs of adult men (6, 8, 10, 104) and dogs (18). The same change was observed in neonatal lambs and 1-month-old sheep in the present study. No attempt was made to determine whether the increase in cardiac output of the lambs differed quantitatively from that of the sheep. The only clear difference was that increases in both heart rate and stroke volume contributed equally to the increase in cardiac output in lambs whereas a decrease in heart rate occurred during hypercapnia in the sheep. The picture of a mature response is supplemented by the observation of Stahlman *et al.* (117) that peripheral vasodilatation occurs during hypercapnia in neonatal lambs.

The mechanism that leads to increased tissue perfusion during hypercapnia seems to

longer than in adult rats (135). Observations on different mammals show that the activities of many enzymes involved in oxidative energy production in the liver increase after birth (30). It would not be surprising if such a change occurs also in the heart. The difference in cardiac response to hypoxia between newborn and adult mammals may possibly be due to different enzyme patterns. A comparative study of the enzyme patterns of hearts of newborn and adult mammals would possibly shed some light on the autoregulatory system of the heart.

The most important finding of this study was that the cardiac output of the lambs did not increase during hypoxia when metabolic acidosis prevailed. This was demonstrated by the series of lambs in which increasing degrees of metabolic acidosis were measured (Fig. 7). When the BE exceeded -5 meq/l., the cardiac output always increased. At a lower BE the cardiac output increased at the beginning of the hypoxia experiment and decreased later (Fig. 12). At a BE of less than -10 meq/l. it remained unchanged or decreased. In this last group the cardiac output was low already initially (Fig. 6). The reason for this variation of the cardiac output during hypoxia in severe metabolic acidosis may be a lowered oxygen transport to the myocardium. It is tempting to think that the initially low output and hypoxia would have caused more rapid progress of metabolic acidosis which in turn would have reduced the cardiac output. However the present series did not support this idea because the development of acidosis was similar in all hypoxia groups. The observed decreased cardiac output during hypoxia associated with severe metabolic acidosis agrees with the observation of Downing *et al.* (37) that ventricular function is depressed in this condition. They also found that hypoxia alone depresses the ventricular function slightly. However increased ventricular work is not necessarily required for increased cardiac

output during hypoxia if the peripheral resistance decreases sufficiently.

There were some age differences between the different groups used in the hypoxia experiments (Table III). The mean ages in groups A, B, and C were 7.2, 6.0 and 5.1 days, respectively. These age differences were not responsible for the differences found in the cardiovascular response to hypoxia because for instance omission of the oldest lamb from group A would have reduced the mean age to that of group B and led to a greater average increase in cardiac output.

The heart rate tended to increase somewhat during hypoxia but the change was not significant. There were large individual variations in the heart rates, and correspondingly the stroke volumes varied greatly in the lambs. The large changes in heart rate possibly indicate variations of the vegetative tone during the experiments. This statement is in agreement with the observations of Harrison *et al.* (59) that procedures which change the vegetative balance of the cardiac innervation may alter the heart rate without affecting the cardiac output. The cardiac output is the most important variable controlled by the organism and possible changes in heart rate will be compensated for by changes in stroke volume. According to these results, the heart rate cannot be considered an accurate indicator of flow conditions in an individual suffering from hypoxia.

An increased degree of metabolic acidosis did not significantly alter the initial heart rate, and the response to hypoxia was exactly the same: a slight increase as in milder acidosis. The variation of the heart rate was greater in mild acidosis than in severe acidosis. These observations on the heart rate in lambs during hypoxia seem to differ from observations on infants suffering from respiratory distress, for infants with the most severe conditions have the highest heart rates (1,4).

The central blood volume increased in parallel with cardiac output in hypoxia. This

the heart rate. Right of the nine lambs of this series were anesthetized and hence the heart rate may have been influenced by the drug.

The significant decrease in the ratio SV/CBV in lambs with metabolic acidosis may be due to decreased ventricular performance, e at a given CBV the stroke volume cannot be maintained. This interpretation does not agree with the finding of Downing *et al.* (37) that metabolic acidosis does not significantly decrease the ventricular function of neonatal lambs. Simultaneous measurement of aortic pressure would undoubtedly have given information about the ventricular function.

The decrease in cardiac output has been explained to be due to lowered glucose uptake by the myocardium (47, 49, 95) or to decreased oxygen supply to the myocardium resulting from a Bohr shift caused by acidosis. All the experiments of the acidosis series lasted more than two hours, and it is possible that the myocardial glycogen stores were reduced by anaerobic glycolysis. Depletion of myocardial glycogen would depress cardiac function by reducing the immediate glucose supply. Clarification of this aspect awaits further experiments.

Metabolic acidosis lowered the central blood volume in most experiments. This observation indicates that blood must have shifted from the lungs to the peripheral vascular beds. This is probably due to a general vasodilatation in metabolic acidosis.

CLINICAL ASPECTS

The conditions which were investigated in the present study are observed in respiratory distress and other clinical conditions accompanied by gas exchange disorders. The sequelae of impaired gas exchange hypoxia and metabolic acidosis also increase pulmonary vascular resistance (105). In acute asphyxia this tension is opposed by more oxygenated

blood which enters the pulmonary circulation from the aorta via the arterial duct (96). If hypoxia continues in spite of this, increased pulmonary vascular resistance reopening of the arterial duct and decreased aortic pressure lead to the pulmonary hypoperfusion (32). This is a condition with impaired gas exchange in the lungs which can be corrected only by a physician, if at all.

The present study shows that the oxygen transport is limited in severe metabolic acidosis not only by impaired pulmonary function but also by suppressed cardiac function. Furthermore, the stimulating effect of arterial hypoxia on the heart observed in normal acid-base conditions is not observed in metabolic acidosis. The hypoxic stimulation of the cardiac output seems to be depressed already at a BE of -5 meq/l. The response of cardiac output to hypoxia when the BE was nearly normal was twofold at best.

The usual treatment for neonatal asphyxia consists of positive pressure ventilation which has been observed to open atelectatic parts of the lungs (96). An increased oxygen partial pressure helps to overcome the effects of decreased pulmonary diffusion. Treatment with alkali-glucose infusion according to Usher (124) has been demonstrated to decrease the pulmonary vascular resistance (100). The present study shows that a normal standard bicarbonate level is required to maintain a normal cardiac output. Thus correction of metabolic acidosis improves both cardiac function and pulmonary perfusion. Also hypoxic stimulation of the heart is corrected by reconstitution of a normal standard bicarbonate level.

In contrast to metabolic acidosis, hypercapnia stimulated the cardiac function. This happened also in the lambs with BE of less than -10 meq/l. A moderately increased level of carbon dioxide may therefore be considered advantageous for the circulation during asphyxia, because it is known to decrease vascular resistance in peripheral and

be present already in lambs at term. The results of Amali *et al* (8) indicate this, because they recorded increased carotid femoral and umbilical arterial flows during hypercapnia. The mechanism leading to increased cardiac output seems to be dependent on the function of the sympathetic nervous system (92). At least the adrenals of lambs at term are known to respond to asphyxia as well as the adrenals of older sheep (23).

Metabolic acidosis seemed not to depress the cardiac response to hypercapnia. There were two lambs with B.E. of less than -10 meq/L. and the cardiac output increased to the same extent in these as in lambs with only moderate metabolic acidosis. This result indicates that an increased level of carbon dioxide in the blood is a more potent stimulator of the heart than a low oxygen content.

The different responses of the cardiac output in hypercapnia and metabolic acidosis indicate that a decrease in pH does not alone determine the cardiac function in an organism. Variations of pCO_2 and standard bicarbonate must therefore have specific effects in all cells or in some receptor cells. The effect of carbon dioxide is the sum of a direct depressant effect on the myocardial function (15) and an increased sympathetic discharge to the heart (92). The influence of the latter is dominant.

The appearance of a total A-V block in a lamb with severe metabolic acidosis during hypercapnia shows that the rhythm of the neonatal heart is probably as sensitive to high carbon dioxide pressure as the rhythm of the adult heart (81). No arrhythmias occurred in lambs with only moderate metabolic acidosis. Further studies are required to clarify in detail how metabolic acidosis combined with hypercapnia affects heart function.

EFFECTS OF METABOLIC ACIDOSIS

The lambs in which metabolic acidosis developed were younger than those in which it

did not (Table III). It seemed to develop more easily in lambs under chloralose anesthesia. The only clearly defined cause of its development was the artificial hypoxia which clearly decreased the standard bicarbonate level (Tables VII and VIII). In many cases, however its origin remained obscure. The lambs which developed metabolic acidosis must have had an anaerobic metabolism which led to increased lactic acid concentrations. No noticeable arterial hypoxia (S_{aO_2} less than 90 per cent) was detected in these cases. Thus, the explanation must be something like that given by Graven *et al* (50) the lactic acid concentration of premature infants increases easily during activity and decreases afterwards, but less rapidly than in adults. Some lambs with metabolic acidosis, especially those under chloralose anesthesia, breathed rapidly and shivered. The shivering stopped or lessened when the anesthesia was deepened. Rapid distressed breathing continued in many cases in spite of apparently sufficient anesthesia. This may be the physical activity which produced lactic acid. If this is true the development of metabolic acidosis indicates that the mechanisms responsible for increased tissue perfusion during physical activity are not mature in neonatal lambs. It is known that physical exercise trains the circulation to effect an appropriate distribution of blood. Therefore it is reasonable to assume that newborn animals require some physical activity before the circulation can adapt itself to greater demands.

The effect of metabolic acidosis was the same as reported for adult dogs (18, 49). The cardiac output decreased by nearly 40 per cent for a decrease of 10 meq/l. in B.E. The arterial pCO_2 decreased at first with B.E. but then remained unchanged (Table XI). A low pCO_2 may also have decreased the cardiac output (18).

The variation of the cardiac output was mainly due to a decrease in the stroke volume although there was a slight decrease also in

be heart rate. Eight of the nine lambs of this series were anesthetized and hence the heart rate may have been influenced by the drug.

The significant decrease in the ratio SV/CBV in lambs with metabolic acidosis may be due to decreased ventricular performance i.e. at a given CBV the stroke volume cannot be maintained. This interpretation does not agree with the finding of Downing *et al.* (37) that metabolic acidosis does not significantly decrease the ventricular function of neonatal lambs. Simultaneous measurement of aortic pressure would undoubtedly have given information about the ventricular function.

The decrease in cardiac output has been explained to be due to lowered glucose uptake by the myocardium (47, 49, 95) or to decreased oxygen supply to the myocardium resulting from a Bohr shift caused by acidosis. All the experiments of the acidosis series lasted more than two hours, and it is possible that the myocardial glycogen stores were reduced by anaerobic glycolysis. Depletion of myocardial glycogen would depress cardiac function by reducing the immediate glucose supply. Clarification of this aspect awaits further experiments.

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The present study shows that the oxygen transport is limited in severe metabolic acidosis not only by impaired pulmonary function but also by suppressed cardiac function. Furthermore the stimulating effect of arterial hypoxia on the heart observed in normal acid-base conditions is not observed in metabolic acidosis. The hypoxic stimulation of the cardiac output seems to be depressed already at a B.E. of -5 meq/l. The response of cardiac output to hypoxia when the B.E. was nearly normal was twofold at best.

The usual treatment for neonatal asphyxia consists of positive pressure insufflation which has been observed to open atelectatic parts of the lungs (96). An increased oxygen partial pressure helps to overcome the effects of decreased pulmonary diffusion. Treatment with alkali-glucose infusion according to Lohr (104) has been demonstrated to decrease the pulmonary vascular resistance (105). The present study shows that a normal standard bicarbonate level is required to maintain a normal cardiac output. Thus correction of metabolic acidosis improves both cardiac function and pulmonary perfusion. Also hypoxic stimulation of the heart is corrected by reinstitution of a normal standard bicarbonate level.

In contrast to metabolic acidosis, hypercapnia stimulated the cardiac function. This happened also in the lambs with B.E. of less than -10 meq/l. A moderately increased level of carbon dioxide may therefore be considered advantageous for the circulation during asphyxia, because it is known to decrease vascular resistance in peripheral and

pulmonary vascular beds (117) An increased level of carbon dioxide in alveoli improves the pulmonary diffusion capacity for carbon monoxide in man (100)

The opposite effects of hypercapnia and metabolic acidosis on the heart suggest that a decreased pH alone is not disadvantageous. A decrease in the standard bicarbonate level obviously must be corrected in a distressed infant. A moderate increase in the carbon dioxide level does not seem to require corrective measures if it is not a sign of reduced oxygen exchange in the lungs.

Signs of the diving pattern were observed in one lamb during hypoxia. This pattern probably develops also in human infants (6, 108). Apparently this kind of circulatory adjustment occurs in pale infants or infants with cyanotic hands and feet. If it involves large parts of the circulation the condition should probably be treated according to the principles of shock therapy. This includes administration of drugs that promote peripheral vasodilatation in constricted parts of the circulation and cardiac function and measures that effect sufficient oxygenation.

Summary

The aim of the present study was to investigate the cardiovascular responses of neonatal lambs to acute hypoxia, hypercapnia and metabolic acidosis for a clarification of the significance of these states in neonatal asphyxia. Basal circulatory values were measured using the dye dilution method. Another aspect studied was the effect of chloralose on the cardiovascular function of neonatal lambs.

The average basal cardiac output under went an almost significant increase from 200 to 300 ml/min kg between the ages of 36 hours and 8 days and decreased subsequently to 60 ml/min kg in sheep 1. months old. The mean heart rate which was 185 per minute in unanesthetized lambs less than 30 days old, was 140 per minute in the sheep. During this period from one to twelve months the stroke volume decreased from 1.45 to 0.60 ml/kg. CBV changed in parallel with the cardiac output. It increased from 18 to 28 ml/kg between the ages of 36 hours and 9 days and decreased to 12 ml/kg in sheep 1. months old. The appearance time increased linearly from 0.1 to .9 seconds during the same period. Evidence was found that AT is directly proportional to the ratio of (CBV to cardiac output).

Chloralose was found to increase the mean heart rate of lambs less than 30 days old from 185 to 40 per minute. Concurrently the stroke volume and ratio SV/CBV decreased. The anesthetic did not have any effect on the cardiac output, central blood volume or appearance time.

During acute arterial hypoxia (S_aO_2 67 per cent on average) induced with 10 per cent oxygen in nitrogen, the mean cardiac

output of the lambs increased by 31 to 33 per cent when the acid-base conditions were normal. When moderate metabolic acidosis was present (B.E. -5 to -10 meq./l.) the mean cardiac output did not rise significantly during hypoxia. If an increase occurred in an individual lamb, a return to the normal output or a lower output occurred within 10 minutes. In severe metabolic acidosis (B.E. less than -10 meq./l.) the cardiac output decreased during hypoxia almost significantly. This change was due to a decreased stroke volume.

The heart rates of the lambs increased insignificantly during acute hypoxia; the degree of metabolic acidosis did not influence this response. The reliability of heart rate as an indicator of flow conditions during hypoxia is discussed. Central blood volume varied in parallel with cardiac output during hypoxia.

The response of sheep over 8 months old to hypoxia was clearly stronger than that of neonatal lambs with a normal acid-base balance. When the mean arterial oxygen saturation was 67 per cent, the cardiac output increased by 63 per cent in the sheep. This was due to an increase in the stroke volume.

Acute hypercapnia (p_iO_2 76 mmHg on average) caused the cardiac outputs of lambs to increase by 97 per cent on average. Increases of both stroke volume and heart rate contributed equally to this change. Metabolic acidosis did not seem to depress the cardiac response to hypercapnia, because also lambs with B.E. less than -10 meq./l. showed increased cardiac outputs. Central blood volume increased during hypercapnia. Chloralose influenced the cardiac response to hypercapnia

almost significantly by suppressing the increases in both cardiac output and heart rate. The cardiovascular changes resulting from hypercapnia in sheep 12 months old differed from those in neonatal lambs in that the heart rates decreased in the sheep but increased in the lambs.

Metabolic acidosis developed during the hypoxia experiments and also spontaneously in the lambs. The mechanism of its spontaneous development is discussed. A decrease of 10 meq/l in B.E. lowered the cardiac

output by almost 40 per cent. This was mainly due to a decrease in the stroke volume.

The clinical application of the knowledge gained in this study is discussed. The results indicate that prevention or correction of metabolic acidosis improves the cardiac function in addition to improving the pulmonary perfusion as observed by other workers. Both of these effects increase the transport of oxygen from the lungs to the tissues. Moderate hypercapnia may even be favorable from the standpoint of cardiovascular function.

Acknowledgements

The present investigation was carried out at the Cardiorespiratory Research Unit and the Department of Physiology University of Turku, in 1965-67. My thanks are due to the staffs of these institutions for their co-operation and support during the study.

I am deeply grateful to my chief, Professor Toomas Peltonen, M.D. Head of the Children's Hospital, University of Turku, and to Associate Professor Leo Hirvonen, M.D. Head of the Cardiorespiratory Unit. They have investigated fetal and neonatal cardiorespiratory phenomena for over ten years and created the present facilities for studies in this field in Turku. Their support has been of great value.

My thanks are due also to Professor Kaarlo Hartiala, M.D. Head of the Department of Physiology of which the Cardiorespiratory Unit is a section, for his interest in my work.

I also wish to express my thanks to Mr. Eikki Sotni, Ph.D., for his help and advice in the construction of the dye dilution equipment

and to the medical students who assisted me during the experiments.

I am grateful to Mrs. Seija Koskinen, Ph.D., for the statistical analyses, to Mrs. Laura Karkola, M.A., for help in collecting the literature, and to Miss H. Aaltonen for help in the preparation of the manuscript.

I am indebted to Mr. E. R. Korte Ph.D., for his revision of the manuscript.

Läike OY medicinal factory Turku, commissioned its art department to draw the figures of this publication. I wish to thank the directors of the company and the artists for this assistance.

A research stipend received from the Lasten tautien Tutkimussäätiö in the early stages of this study is gratefully acknowledged. Grants awarded by the Sigrid Jusélius and the Yrjö Jahnsson Foundations to the Cardiorespiratory Research Unit have also supported my work, for which I am grateful.

Turku, April, 1969

Aulis Korvicko

almost significantly by suppressing the increases in both cardiac output and heart rate. The cardiovascular changes resulting from hypercapnia in sheep 12 months old differed from those in neonatal lambs in that the heart rates decreased in the sheep but increased in the lambs.

Metabolic acidosis developed during the hypoxia experiments and also spontaneously in the lambs. The mechanism of its spontaneous development is discussed. A decrease of 10 meq/l in BF lowered the cardiac

output by almost 40 per cent. This was mainly due to a decrease in the stroke volume.

The clinical application of the knowledge gained in this study is discussed. The results indicate that prevention or correction of metabolic acidosis improves the cardiac function in addition to improving the pulmonary perfusion as observed by other workers. Both of these effects increase the transport of oxygen from the lungs to the tissues. Moderate hypercapnia may even be favorable from the standpoint of cardiovascular function.

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EXPERIMENTAL STUDIES ON
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UTILIZING WHOLE-BODY FREEZING

BY P YNGVE HÖRNB�AD

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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The present dissertation is a summary of the following papers

- I Hornblad, P Y & Larsson K. S. Studies on closure of the ductus arteriosus. I Whole body freezing as improvement of fixation procedures. *Cardiologia (Basel)* 51 231 1967
- II Hornblad P Y & Larsson, K. S. Studies on closure of the ductus arteriosus. II Closure rate in the rat and its relation to environmental temperature. *Cardiologia (Basel)* 51 742, 1967
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Reference will be made to these papers using the Roman figures as listed above

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INTRODUCTION

The direct communication between the pulmonary trunk and the aorta in the foetus is known as the ductus arteriosus. Although this structure was described by Galen as early as the second century A. D. its function was not known until Harvey in 1628 introduced the modern concept of the blood circulation (8). In the foetus, the ductus arteriosus permits blood from the right ventricle to enter the systemic circulation without passing through the lungs. It is of great importance that the circulation through the ductus is arrested after birth to establish complete separation of the pulmonary circulation from the systemic. This is mediated by

closure of the ductus a process which is not fully understood. In human beings, the ductus exceptionally fails to close resulting in a condition which is known as a patent or persistent ductus arteriosus. Its aetiology is still unknown but it is interesting to note that it is not infrequently associated with other malformations (53). Even if a patent ductus arteriosus can nowadays be corrected surgically at a low risk (??) it is highly desirable to diminish its incidence. A prerequisite is, however, to obtain further basic information about the ductal morphology and physiology which can only be achieved experimentally.

SURVEY OF THE LITERATURE

In this section the most pertinent literature on closure of the ductus arteriosus will be briefly surveyed. For more comprehensive reviews, reference is made to publications by Swenson (84), Sciaccia & Condorelli (78) and van Ingen (42).

Morphology of the ductus arteriosus

The ductus arteriosus in human beings was early found to differ morphologically from the aorta and the pulmonary trunk (48). The full term ductus has frequently been ascribed a thick, loose wall in comparison to the aorta, with a narrowed lumen lined by a prominent intima exhibiting protrusions (7, 28, 38, 43, 84). Its nature of a muscular artery (12) is now generally accepted. A similar ductal morphology has been described in the guinea pig (45, 65), rat (42, 60) and rabbit (80). Fixation procedures have occasionally been suggested to cause

artefacts of the ductal morphology (6, 63, 88). In an attempt to diminish these artefacts by distension of ductuses from autopsy cases during the fixation period, a very thin wall, an unconsiderable intima without protrusions, and a rounded lumen were found (6).

Mode of ductal closure

Closure of the ductus arteriosus has been described as an initial passive phenomenon, succeeded by proliferative processes of the wall. Compression of the ductus was one of the explanations of its passive closure (53, 59). Kinking and twisting of the ductus has also been suggested to cause closure (51, 77). A valve-like formation of the ductus has been stated to provide an instantaneous arrest of the blood flow (71, 83). However, closure of the ductus has also been reported to result from proliferative processes—occurring already prenatally—

without preliminary passive occlusion (38-48, 78).

According to the current concept, closure of the ductus arteriosus can be divided into two distinct phases (8, 45-58). The primary phase consists of a contraction of the ductal wall with narrowing of the lumen, and the secondary phase of an intimal proliferation causing final obliteration. These phases are usually denoted as the physiological and the anatomical closure, respectively arising from the terms which Gérard (27) introduced in 1900 "l'occlusion physiologique" and "l'oblitération anatomique". However Gérard believed the physiological closure to be passive. As early as 1856, Virchow (87) put forward the hypothesis that an active muscular contraction of the ductal wall was responsible for an early closure. Von Hayek (34) and later Meyer & Simon (56) made a detailed study of the morphological prerequisites for muscular contraction. It is generally agreed that the anatomical phase of ductal closure consists of intimal proliferation, degeneration and atrophy of muscular elements with subsequent sclerosis (38, 43-62). Augmentation of elastic tissue (43, 76) and deposition of mucoid substances (38, 42, 78-86) are other factors which have been ascribed crucial importance.

Rate of ductal closure

The concept ductal closure rate has not been used earlier since the reduction in the ductal lumen has not been examined at regular and frequent intervals after birth. In morphological studies the time after birth for closure of the ductus has been determined from disappearance of the lumen. In physiological studies, on the other hand, closure of the ductus has been considered to exist when arrest of the blood flow was observed.

Closure of the human ductus was believed to occur instantaneously on birth, when mechanical factors were suggested to be responsible for passive closure (51, 53, 59, 71, 77, 83). A closure process over a long period has on the contrary been reported when intimal prolifera-

tion alone was proposed to cause closure (38, 48). Physiological studies in human beings have also indicated that blood may flow through the ductus for several days after birth (4, 16, 23, 40, 72). Reports of a rapid closure, based on morphological investigations in the guinea-pig (45) rat (42) and rabbit (80) and on physiological studies in the lamb (8) support the view of a muscular contraction of the wall. Contrarily, a considerable blood flow through the ductus has been demonstrated in physiological investigations for up to 2 days in the lamb (21) calf and foal (1) and during the first day in the dog (25). In the guinea-pig as well, late closure has been observed morphologically (37, 63).

Anatomical closure has been reported to be complete in one up to several months in human beings (38, 43, 53, 62). Similar periods are given in the pig (76) and calf (33). In the dog (39) cat (40) guinea-pig (45) and rat (42) complete obliteration has been noted 1-4 weeks after birth.

Cause of ductal closure

The common cause of different modes of a passive ductal closure has been ascribed to the onset of respiration. Displacement of mediastinal organs was considered to cause compression (53, 59) kinking and twisting of the ductus (51, 77) and the ductal valve (71, 83) was believed to close under the influence of haemodynamic changes. Aeration of the lungs has also been regarded to produce lowering of the distension pressure in the ductus, which would simply enable the distended ductal wall to contract (70).

The discussed causes of an active contraction of the ductal wall do not have a common denominator. Stimulation of the left vagus nerve has been used to elicit ductal contraction in the guinea-pig (9). Nearly 30 years ago, good evidence of a relation between oxygen and ductal closure was presented by Kennedy & Clark (43, 46). An increase in oxygen saturation of the

INTRODUCTION

The direct communication between the pulmonary trunk and the aorta in the foetus is known as the ductus arteriosus. Although this structure was described by Galen as early as the second century A.D. its function was not known until Harvey in 1628 introduced the modern concept of the blood circulation (8). In the foetus the ductus arteriosus permits blood from the right ventricle to enter the systemic circulation without passing through the lungs. It is of great importance that the circulation through the ductus is arrested after birth to establish complete separation of the pulmonary circulation from the systemic. This is mediated by

closure of the ductus, a process which is not fully understood. In human beings, the ductus exceptionally fails to close resulting in a condition which is known as a patent or persistent ductus arteriosus. Its aetiology is still unknown but it is interesting to note that it is not infrequently associated with other malformations (63). Even if a patent ductus arteriosus can nowadays be corrected surgically at a low risk (??) it is highly desirable to diminish its incidence. A prerequisite is, however, to obtain further basic information about the ductal morphology and physiology which can only be achieved experimentally.

SURVEY OF THE LITERATURE

In this section the most pertinent literature on closure of the ductus arteriosus will be briefly surveyed. For more comprehensive reviews reference is made to publications by Svensson (84), Sciacca & Condorelli (78) and van Ingen (42).

Morphology of the ductus arteriosus

The ductus arteriosus in human beings was early found to differ morphologically from the aorta and the pulmonary trunk (48). The full term ductus has frequently been ascribed a thick, loose wall in comparison to the aorta, with a narrowed lumen lined by a prominent intima exhibiting protrusions (7, 28, 38, 43, 84). Its nature of a muscular artery (12) is now generally accepted. A similar ductal morphology has been described in the guinea pig (45, 65), rat (42, 60) and rabbit (80). Fixation procedures have occasionally been suggested to cause

artefacts of the ductal morphology (6, 63, 88). In an attempt to diminish these artefacts by distension of ductuses from autopsy cases during the fixation period, a very thin wall, an inconsiderable intima without protrusions, and a rounded lumen were found (6).

Mode of ductal closure

Closure of the ductus arteriosus has been described as an initial passive phenomenon, succeeded by proliferative processes of the wall. Compression of the ductus was one of the explanations of its passive closure (53, 59). Kinking and twisting of the ductus has also been suggested to cause closure (51, 77). A valve-like formation of the ductus has been stated to provide an instantaneous arrest of the blood flow (71, 83). However, closure of the ductus has also been reported to result from proliferative processes—occurring already prenatally—

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blood perfusing the ductus in the lamb was later shown to cause a contraction of its wall, whereas a decrease in oxygen saturation caused dilatation of a partially contracted ductus (3 10 68). Additional support for the role of oxygen is obtained by the fact that the physiological closure is affected only by a reduced oxygen supply. Administration of nitrogen has resulted in failure of the guinea pig ductus to close or reopening of a partially closed ductus *in vivo* (46) and *in vitro* (47). Similarly under hypoxia, a delay in ductal closure has been reported in the guinea pig (67) and dog (88) and widening of the ductus has been described in the lamb (10) and the human being (44 57).

It has, on the other hand, been stated that the ductus will also contract at a low saturation

during asphyxia (10). Liberated catecholamines have been suggested to cause closure of the ductus in this condition. Administration of catecholamines has also been demonstrated to cause constriction of the lamb ductus, both *in vivo* (10) and *in vitro* (47). A direct effect of catecholamines on the ductus *in vivo* has nevertheless also been denied (79).

Considerable interest has been focused on kinins in adaptation of the circulation to extra-uterine life (54 74). Recently it has been demonstrated that bradykinin is very potent in causing constriction of the calf and lamb ductus arteriosus *in vitro* (24).

An interference with the anatomical closure seems to occur when newborn rats are treated with aminoacetonitrile (41).

PRESENT INVESTIGATIONS

OBJECT OF THE STUDIES

It is obvious from the reviewed literature that different concepts still exist concerning the ductal morphology as well as the mode and time of physiological closure of the ductus arteriosus. Moreover no conclusive cause of the physiological closure has been presented.

Consequently it seemed expedient to perform additional studies on closure of the ductus arteriosus. The present investigations were strictly limited to experimental studies of the physiological phase, and the aims were

- 1 To apply a morphological technique which allows instantaneous and permanent immobilization of the ductus arteriosus.
- 2 To study the mode of ductal closure in different species on the basis of morphological changes occurring prenatally and at birth.
- 3 To determine the rate of ductal closure in different species.
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METHODOLOGICAL

Animals

In the present investigations, experimental animals of five species were used: pig (III), guinea-pig (III—VI), rabbit (III—IV), rat (I—VI) and mouse (III, IV). All these species—except the mouse—have been studied in earlier investigations of the ductus arteriosus. Comparisons with earlier results were therefore possible. Moreover the selected species exhibit a different degree of development at birth, with respect to e.g. maturity of the nervous system, locomotor organs and temperature regulation.

All animals were obtained from commercial suppliers, except for the mice which were injured at the laboratory (49).

Animals housed in the laboratory were fed on standardized diets (I, III). In the rat and mouse pregnancy was diagnosed from the presence of spermata in the vaginal smear and finding of a vaginal plug, respectively (I—III). In the pig and rabbit, the day of mating was given by

the supplier. The time of mating of the guinea-pigs used in the embryological experiment (IV) was established to within two days. Accurate embryonic age was thus secured for the prenatal study (IV) and facilitated predicting the time of delivery in the other experiments (I—III, V—VI). Guinea-pigs with known date of mating were not, however, available in adequate numbers for the investigation on the maternal submitted to caesarean section near term (VI). The method of determining approaching delivery by observing the degree of symphysiolysis (66) proved to be satisfactory.

Experimental procedures

In the studies on the closure rate (II, III) and the morphology postnatally (II, III &) the newborns were kept under conditions which can be considered as applying in nature. In the pig and guinea-pig, this was ensured by allowing the mothers to nurture the newborns in their

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temperature until sacrifice. This could not be done in the rabbit, rat and mouse as these species—when disturbed during delivery—will not nurture their offspring and may even injure the newborns. To prevent the loss of body temperature in newborn rats and mice (26–36) they were placed in glass tubes incubated at 37°C and 36°C, respectively which is close to the normal body temperature of adult rats and mice (29). Newborn rabbits were brought to an incubator at 30°C although the body temperature of adult animals is close to 39°C (29). As rabbits normally deliver out-of-doors, it was considered that the temperature would have been lower in the burrow.

Caesarean section was always performed under ether anaesthesia (IV–VI). General anaesthesia could be kept superficial for up to 1 hour by the addition of a local anaesthetic in the abdominal wall (VI).

The effect of hypothermia on the ductal closure rate was studied in the rat (II). The newborns were placed in ventilated glass tubes, which were incubated at 37°C, 30°C and 21°C. The animals were sacrificed at the age of 4 hours, or at definite intervals earlier. To study the influence of hypoxia on the ductal closure rate (V, I) newborn rats were kept in glass tubes at 37°C in an atmosphere of 8 ± 1 per cent of oxygen in nitrogen, while control animals were allowed to breathe air. They were sacrificed at definite intervals up to 4 hours. — To determine the effect of inhaled air and nitrogen on closure of the ductus arteriosus in the guinea pig (VI) full term foetuses were delivered by caesarean section under lukewarm saline. They were raised to the surface and allowed to breathe air or supplied with nitrogen in an inverted glass funnel for periods of 5 minutes before sacrifice.

The effect on the heart rate of hypothermia (II) and hypoxia (VI) was studied in the rat. Newborns were incubated in glass tubes, and by means of special electrodes, electrocardiographic recordings were made at 15 minute intervals during 4 hours after birth. The heart rate was determined from 10 consecutive heart cycles.

Sacrifice was performed by whole body freezing (I) of all animals used in investigations II–VI. In addition to animals sacrificed immediately on birth, newborns of the pig were sacrificed at intervals of up to 24 hours after birth, those of the guinea pig up to 12 hours, and those of the rabbit, rat and mouse at intervals up to 4 hours after birth. Newborns of the rat and mouse were frozen in isopentane cooled by dry ice (–78°C–30). Newborn pigs, guinea pigs and rabbits were frozen in liquid nitrogen (–196°C–30) as it was very inconvenient to cool isopentane in amounts necessary for their effective freezing. Dislocation of the atlas, followed by freezing or ordinary formalin fixation after storage or after dissecting out the ductus, was also used for comparisons between different fixation techniques (I).

Freeze fixation was obtained simultaneously after whole body freezing which allowed transfer of cryostat sections to slides with the original structure of the tissues preserved. The morphology of the freeze-fixed tissue was satisfactory as no freezing artefacts could be observed in the light microscope. — A series of sections at close intervals was prepared throughout the ductus, in addition to sample sections. The series was well stained in haematoxylin and eosin. Selected sections were successfully stained for elastic fibres in Weigert's resorcin fuchsin, and the collagen fibres were visualized in Masson's trichrome stain (17). Cryostat sections were also used for the microradiographical investigations (V) by affixing them to celloidin-coated Eastman Kodak High Resolution Plates. These were exposed at 1.2–1.6 kV and developed in Kodak D19b. Only qualitative analysis under the light microscope was made.

Microscopical examination of the ductal morphology was undertaken, and the dimensions of the lumen and wall thickness of the ductus were recorded (I–VI). The section of the ductus arteriosus showing the smallest lumen was selected for microscopical measurements of the outer and inner diameters. The measurements were made at the narrowest point of the lumen, and in the plane perpendicular to the narrow est

point. The arithmetic means of these measurements were used for calculation of mean values of inner diameter and wall thickness in the different experimental groups. All dimensions were determined under the light microscope using a measuring eye-piece. This allowed measurements of the ductus in the pig, guinea pig and rabbit to be made with a precision of $\pm 20 \mu$, and in the rat and mouse of $\pm 8 \mu$. Tabulated mean values of inner diameter and wall thickness were rounded off to the nearest 10μ in the pig, guinea-pig and rabbit, and to the nearest 5μ in the rat and mouse.

For comparisons between the different species with respect to the degree of ductal closure

use was made of the ratio mean value of the wall thickness to the inner diameter of the ductus— $\frac{\text{wall thickness}}{\text{inner diameter}}$ (III–IV–VI). This ratio was also used as a complement to comparisons between the mean inner diameter in the different experimental groups within one species (VI).

For statistical comparisons between the mean values in the different experimental groups, a one-tailed analysis of "Student's *t* test" (61) was performed. In all investigations, the experimental groups were provided with animals in a regular order to obtain an even distribution of possible variations within the litters.

RESULTS

Efficiency of whole-body freezing

When whole-body freezing (I) was used for sacrifice and fixation (II–VI) the central vessels displayed a wide, rounded lumen with a smooth inner surface, which was lined by widely separated, flat endothelial cells. The thin media was composed of straight elastic lamellae and interspersed slender muscle cells. This was in striking contrast to the aescular morphology after formalin fixation (I) which was characterized by deformed and narrowed lumen, lined by thick, closely packed endothelial cells, and a broad media showing pronounced intermingling of the elastic lamellae and thick cells in between. Particularly the ductus arteriosus of newborns exhibited—when fixed in formalin or subjected to mechanical stimulation (I)—severe distortions as described above, which were not observed after whole-body freezing.

The ductal morphology seen after whole-body freezing revealed, moreover, that considerable differences were present shortly after birth, whereas the morphology of the aorta and pulmonary trunk was unchanged (II–III). This difference could be demonstrated within few minutes of birth in the guinea-pig and rabbit.

Morphological observations on the ductus arteriosus

At birth the ductus arteriosus of whole-body frozen animals showed, in all five species, rounded lumen with a smooth inner surface lined by a single layer of flat endothelial cells (I–III–V–VI). The subendothelial zone was of inappreciable extent in the rat and mouse, whereas in the pig, guinea-pig and rabbit, fibroblasts and elastic and collagen fibres were visible most prominent in the rabbit. The media was composed of straight elastic lamellae, alternating with thin layers of slender smooth muscle cells and occasional fibroblasts. The number of lamellae varied with the species (III). The inner and outer parts of the media had the same dry mass concentration (V). No distinct adventitia could be separated from the surrounding loose connective tissue. This layer was therefore excluded when the wall thickness was measured.

Comparisons between the ratio $\frac{\text{wall thickness}}{\text{inner diameter}}$ revealed that newborns of the pig, guinea pig and rat had the same relative wall thickness of 0.07 (III). Newborns of the rabbit had a higher

temperature until sacrifice. This could not be done in the rabbit, rat and mouse as these species—when disturbed during delivery—will not nurture their offspring and may even injure the newborns. To prevent the loss of body temperature in newborn rats and mice (96, 36) they were placed in glass tubes incubated at 37°C and 36°C respectively which is close to the normal body temperature of adult rats and mice (29). Newborn rabbits were brought to an incubator at 30°C although the body temperature of adult animals is close to 39°C (29). As rabbits normally deliver out-of-doors, it was considered that the temperature would have been lower in the burrow.

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Microscopical examination of the ductal morphology was undertaken and the dimensions of the lumen and wall thickness of the ductus were recorded (I–VI). The section of the ductus arteriosus showing the smallest lumen was selected for microscopical measurements of the outer and inner diameters. The measurements were made at the narrowest point of the lumen and in the plane perpendicular to the narrowest

umbilical circulation were kept for 5 minutes in nitrogen after an initial period in air (VI)

In the rat, a significant delay in the ductal closure rate was recorded when newborns were kept in atmosphere of reduced oxygen concentration (VI) or when the environmental temperature was lowered to 21°C (II). In animals 4 hours of age, the lumen was nevertheless

reduced to less than 5 per cent. A decrease in the environmental temperature to 30°C did not affect the closure rate (II). On the other hand, the observed decrease in the heart rate under hypothermia (II) showed an almost linear correlation to the environmental temperature. A significantly depressed heart rate was also recorded under hypoxia (VI).

DISCUSSION

Whole-body freezing in studies of the ductus arteriosus

The blood shunt through the ductus arteriosus at different stages of ductal closure has been studied as a part of foetal adaptation to extra-uterine life. Different techniques have been used, such as direct measurements of the blood flow (4) blood oxygen analyses (23-58) cine radiography (8) dye dilution (16, 31-64) and isotope tracing (25).

For studies of the ductal closure *per se* on the other hand, it is appropriate to record the changes in the ductal lumen by direct measurements of its inner diameter. Until whole-body freezing was used for sacrifice and fixation, it was not possible to visualize the ductus arteriosus in a state which might reflect its state *in situ* (1). The commonly used technique of immersion fixation after death—preceded in most cases by dissection—is ineffective, as post-mortem contraction of the wall cannot be prevented (1). The risk of fixation artefacts has been apprehended, but the attempts to avoid them by refrigeration and delayed fixation (65-88) were doomed to failure (52). Although distension of the ductus prior to fixation (6) will improve morphology, reliable information about its dimensions cannot be obtained, because of possible overdistension (55). After whole-body freezing, on the contrary it has been demonstrated that the ductus arteriosus of various species exhibits characteristics of emulsified under pressures which can be considered as physiological (13-15, 53-69). More

over the finding in newborns of the guinea-pig and rabbit of very rapid changes in the ductal inner diameter (111) indicates that instantaneous immobilization of the ductus is achieved by this technique. Since the ductus cannot be considered to freeze instantaneously even in such small animal as the newborn mouse the intraluminal pressure seems to be maintained in an unspecified way until the ductal wall is frozen. The results in the pig indicate that the efficiency of whole-body freezing is not limited by the size of the animals used in this study. This implies that reliable information about actual dimensions of the ductus arteriosus before birth and during its closure can be obtained in different species. Minor deviations from the normal closure process, e.g. induced by experimental factors, can also be visualized by use of the whole-body freezing technique.

Mode of ductal closure

Observations of decreased outer diameter and increased wall thickness, accompanied by widening of the elastic lamellae, remodelling of the inner media and central displacement of the intima (11-111) support the generally accepted view that the ductus arteriosus is closed by a muscular contraction of its wall after birth (6, 8, 33-42, 57-62, 82).

The present observation of a progressive growth of the ductal lumen during late intra-uterine life in four species (IV) is contrary to reports of a constant lumen during this period

value, but in some of these animals closure was already initiated (III). Full term rabbit foetuses, on the other hand, also exhibited a relative wall thickness of 0.07 (IV). In the mouse, the newborns (III) had a value of only 0.04 which, moreover, was close to the value of 0.03 found in the rat aorta (IV). In the mouse the ductus and the aorta also displayed similar amounts of elastic fibres, whereas in the other four species, the ductal wall contained definitely less elastic tissue than the aorta (III).

During closure the ductus arteriosus in all five species exhibited similar morphological changes, which moreover were directly correlated to the degree of closure (II-III). With narrowing of the lumen the outer diameter decreased and the wall gained in thickness. At the inner surface the endothelial cells piled up and the media displayed progressive remodelling. The elastic lamellae showed increasing waviness and condensation, most marked centrally. This was very strikingly visualized in the microradiograms (V). The interposed cells became thicker and their circular orientation was changed to a radial one in the inner part of the media. No concomitant change in dry mass concentration was observed (V). During closure, the ductal lumen of the pig, guinea pig and rabbit became deformed by indentations of the wall, indicative of advanced remodelling. This was most conspicuous in the ductus of the guinea pig in which tissue defects in the inner media were easily identifiable in ordinary histological sections (III) as well as in microradiograms (V). In completely occluded ductuses of all species, the endothelial cells were accumulated centrally with formation of a solid cell core. In addition to other intimal structures, they filled up the rounded or slit-like space available inside the constricted media.

Prenatally, during the last part of intrauterine life, an increase in the ductal lumen was found in the guinea pig, rabbit, rat and mouse, whereas an increase in wall thickness could be demonstrated only in the guinea pig and the rabbit (IV). The structure of the wall did not change during this phase and the ductal morphology

of full term foetuses (IV) was indistinguishable from that of newborn animals (III). Dimensions of inner diameter and wall thickness were also of the same magnitude in full term foetuses (IV) and in newborns (III).

Rate of ductal closure

Investigations of the ductal closure rate disclosed that species differences existed (II-III). Newborns of the guinea pig and rabbit showed very rapid closure of the ductus: a narrowing of the lumen to less than 5 per cent could be demonstrated after 2 minutes. Newborns of the pig, rat and mouse showed no such instantaneous closure. In the mouse a corresponding narrowing of the ductal lumen was found after 30 minutes, in the rat only after 1 hour and newborns of the pig did not exhibit the same degree of closure until 2 hours after birth. In the guinea pig and rabbit, complete occlusion of the ductus followed about 30 minutes after birth, while in the mouse disappearance of the lumen was demonstrated only after 2 hours, in the rat after 3 hours and in the pig after 8 hours. Also in the mouse a significant reduction in the ductal lumen was observed at the age of 2 minutes. In the rat, on the other hand, no decrease occurred during the first 10 minutes following birth (III).

Interference with the physiological phase of ductal closure

Closure of the ductus arteriosus could be affected by means of certain experimental conditions (II-VI). In the guinea pig closure was prevented by keeping foetuses—with intact or interrupted umbilical circulation—in an atmosphere of nitrogen (VI). Narrowing of the ductal lumen to about 20 per cent occurred, on the other hand, within 5 minutes in foetuses with an intact umbilical circulation when kept in air and to approximately 2 per cent when the umbilical circulation was interrupted. No significant dilatation of a partially closed ductus was obtained when foetuses with an interrupted

Cause of ductal closure

Of factors which has been proved to induce constriction of the ductus (9, 10, 4, 45, 46, 47, 79) only oxygen and certain vasoactive agents might be relevant in discussing causes of the physiological ductal closure.

The present results (VI) confirm that oxygen causes ductal closure in the guinea-pig (43). Furthermore, the observed delayed closure rate in rats under hypoxia supports the role of oxygen in ductal closure (VI). The mechanism of oxygen action is not, however satisfactorily explained. Its effect has been suggested to be mediated by rise in the oxygen saturation of the blood perfusing the ductus (3, 10, 46, 57, 68). This implies that a reverse shunt through the ductus is initially established, a condition which has been demonstrated in the lamb (20), calf and foal (1). Such an arrangement would also be possible in animals with a slow closure rate, like the pig, mouse and rat (II, III). In addition, it is possible that, in the rat, the usual inactive period of ductal closure coincides with a persisting right-to-left shunt (III). On the other hand, if a high arterial oxygen saturation were to be the cause of ductal closure also in animals in which it takes place almost instantaneously—as observed in the guinea-pig and rabbit—the onset of effective respiration within a few seconds of birth has to be demonstrated.

The experimentally induced delay in closure of the ductus arteriosus in hypothermic and hypoxic rats might be the basis for a brief discussion of the role of catecholamines (II, VI). After oxygen, catecholamines are the most discussed cause of ductal closure (10, 47, 79). No definite conclusions concerning their effect can be drawn from the present investigations. It can nevertheless be surmised that acidosis (18) develops in hypothermic rats (II). Acidosis has also been demonstrated in newborn rats supplied with low oxygen concentration (85), as used in Paper VI. As adrenergic receptors are known to be hindered by lowering of the pH (14) the demonstrated delay in closure rate under hypothermia and hypoxia may indicate a possible

role of catecholamines in ductal closure. However observations *in vivo* (10) and *in vitro* (47) indicate that variations in pH have no effect on closure of the ductus arteriosus. On the other hand, it may also be suggested that hypothermic rats are hypoxic (18). The observed delay in closure rate during hypothermia would then further support the importance of oxygen for ductal closure.

The delay in ductal closure rate observed in rats under hypothermia (II) does not support the suggestion that bradykinin might be of consequence for ductal closure (54, 74). The formation of bradykinin is, in fact, stated to be activated by a decrease in temperature (54).

Clinical interpretation

For morphological studies of the human ductus arteriosus, distension of the ductus prior to fixation (6) seems at present to be the most appropriate technique for its preservation. Using this technique, the ductal morphology in stillborn babies resembles that in newborn animals fixed by whole-body freezing (III). Similar morphological changes to those observed in the animals in the present study (II, III) have been described in the human ductus during its closure (6). It can therefore be assumed that no essential differences do, in fact, exist between the ductal morphology and mode of ductal closure in the human being and in other mammals.

On the other hand, in view of possible overdistension (45) distension fixation will fail to provide reliable data on inner diameter and wall thickness of the human ductus before closure, as well as during its physiological phase. The rate of ductal closure cannot therefore be established in human subjects as in animals (III). It is nevertheless tempting to ascertain the conceivable rate from results of clinical observations. Demonstration of a right-to-left shunt through the ductus during the first hours of life (2, 23, 58, 75) despite a progressively falling pressure gradient (72, 75) indicates that no decrease in inner diameter occurs during this time. After the reverse shunt has been established, there is still a large flow through the ductus.

in the human being (60) narrowing of the lumen in the human being and rat (49, 60) and prenatal closure of the lumen in the guinea pig (78). Growth of the ductus prenatally is in agreement with prevalent views of a large ductal blood flow throughout intrauterine life (11, 50, 81). Additional evidence is afforded by the finding that the ductus has more than half the cross-sectional area of the descending aorta in full term rats (IV).

The observation of a wide ductal lumen in newborns, and especially its dramatic decrease within minutes of birth in the guinea pig and rabbit (III) clearly demonstrates that the physiological closure takes place shortly after birth (45). The prenatal ductal morphology in the guinea pig, rabbit, rat and mouse (IV) and the microradiographical observations in the rat and guinea pig (V) give no evidence of a preparatory process in the media preceding the contraction (37, 56). Nor is there any microradiographical support (V) for formation of excessive amounts of ground substance in the ductal wall during closure (42, 78). The extensive tissue lesions of the inner media observed in some species (III, V) suggest that the ductus is not intended for repeated closure and opening, which has been reported to occur prenatally (50) and has also been demonstrated postnatally under experimental conditions (10, 45, 68). Disappearance of the ductal lumen in all five species as a consequence of central displacement of the intima during the contraction (II, III) demonstrates that already during the physiological phase of closure, a functional anatomical closure is achieved. During the anatomical phase, there is probably merely a consolidation of the tissue.

Rate of ductal closure

No earlier report of the ductal closure rate has been presented for any species, whereas the time for closure of the ductus is given in a number of species, in morphological studies based on disappearance of the ductal lumen (38, 49, 43,

45, 65, 80, 84) as well as in physiological investigations (1, 3, 8, 10, 25, 58, 73) determined from arrest of the blood flow through the ductus.

The present studies have clearly demonstrated that determination of the closure rate has permitted characterization of the ductal closure in different species in a more appropriate way than merely by observing disappearance of the ductal lumen (II, III). Knowledge of the species differences as regards closure rate should be the basis for selection of appropriate species for studies of experimental factors which might interfere with ductal closure. The validity of this concept is borne out by the experiments in the guinea pig when oxygen and nitrogen were supplied, and interruption of the umbilical circulation was performed immediately on delivery and the effects had to be registered within the next few minutes (VI). In a similar experiment in the guinea pig (67) the reduction in oxygen concentration was applied only after 3 minutes—i.e. after the period of most active constriction of the ductus—and the results were not recorded until 24 hours later. In species with slow ductal closure, as in the rat, a significant response to hypothermia (II) and hypoxia (VI) could also be demonstrated by determining the closure rate.

The ductus arteriosus can however be assumed to close functionally before disappearance of its lumen (II). Already on reduction of the inner diameter to 20 per cent—occurring in the guinea pig and rabbit within 2 minutes, in the mouse before the age of 30 minutes, in the rat within 1 hour and in the pig about 2 hours after birth—the corresponding ductal flow is namely decreased to less than 0.2 per cent at a constant pressure gradient. It is unlikely that changes in the pressure gradient will restore any considerable flow, since the flow through a vessel is proportional to the fourth power of its radius, but directly proportional to the pressure gradient (35). Because of lack of knowledge of the ductal lumen in newborns, patency has therefore been ascribed to ductuses exhibiting only a minimal lumen (65, 88).

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for some more hours (9) Demonstration of a measurable left to-right shunt through the ductus only occasionally after the age of 15 hours (2 57 58 64 73) might however indicate that the ductus arteriosus at this time is severely narrowed and even closed in many cases. It therefore seems likely that the human ductus arteriosus will not constrict during an initial period with a persisting right to-left shunt of approximately 3 hours, in contrast to all the species investigated in the present study

Dilatation of the human ductus arteriosus under hypoxia, and subsequent re-establishment of the constriction on recovery of the arterial oxygen saturation (44 57) make it likely that

in human beings as well oxygen is the cause of ductal closure. Occasional observations of delayed closure in prematures, which have low arterial oxygen tension (5 19) further indicate the great importance of oxygen for closure of the ductus arteriosus. There is therefore reason to believe that the cause of ductal closure in human beings and other mammals is identical, although the mechanism is unknown.

As a conclusion, it seems justified to investigate the closure process in animals with respect to prenatal changes in the ductal morphology and postnatal interference with causes of ductal closure, in order to disclose the development of patent ductus arteriosus in human beings.

SUMMARY

In the present studies on closure of the ductus arteriosus in the pig, guinea-pig, rabbit, rat, and mouse, whole-body freezing was used for sacrifice and fixation. With this technique, the ductus is available for morphological studies in a state which can be considered to reflect its state *in vivo*. Examinations of its structure, as well as measurements of inner diameter and wall thickness, are therefore of consequence. The results presented confirm that the technique is valid for animals of different size, at least up to the size of a newborn pig.

In newborns of all species, the ductus arteriosus exhibits a rounded lumen with a smooth inner surface and a thin wall composed mainly of the media, which has straight elastic lamellae and slender interposed muscle cells. Observations of a progressive growth of the ductus during late intrauterine life indicate that its closure is initiated after birth. During closure, the ductus of all species displays similar morphological changes which conclusively indicate that the narrowing is brought about by contraction of its muscle coat. Remodelling of the inner media enables an extensive contraction, and disappearance of the lumen is achieved already during the physiological phase of closure by central displacement of intimal cells.

Species differences exist in the ductal closure rate. The guinea-pig and rabbit exhibit a rapid closure rate of the ductus arteriosus, with a severe narrowing of its lumen already within 2 minutes. Newborns of the mouse and rat, on the other hand, display the same degree of ductal closure only after 30 minutes and 1 hour, respectively. In the pig a corresponding narrowing of the lumen is found only after 2 hours. Complete occlusion of the ductus follows in the guinea-pig and rabbit about 30 minutes after

birth, while in the mouse disappearance of the lumen is observed only after 2 hours, in the rat after 3 hours and in the pig after 8 hours. Information on the ductal closure rate is important for the planning of studies of factors which might interfere with closure.

Additional support has been obtained that oxygen is essential for closure of the ductus arteriosus. The proposed action of oxygen as mediated to the ductal wall by perfusing blood with high oxygen saturation, might be possible in animals with a slow closure rate like the pig, rat and mouse. On the other hand, if this is to apply in animals with an almost instantaneous closure rate—like the guinea pig and rabbit—the onset of effective respiration within a few seconds of birth has to be demonstrated. No definite conclusions can be drawn regarding the effect of catecholamines. Possible acidosis under conditions accompanied by delayed ductal closure rate might, however, indicate that adrenergic receptors are involved in the closure process, while on the other hand no support is obtained for ductal closure caused by bradylum.

Comparisons between the results of the present investigations in animals, using whole-body freezing, and of an earlier reported study in human beings, using distention fixation, indicate that no essential differences do, in fact, exist in ductal morphology and mode of ductal closure between the human being and other mammals. Reported estimations of the blood flow through the ductus arteriosus in babies are, however, consistent only with a considerably lower ductal closure rate in human subjects than that observed in the investigated species. The concept of oxygen as an important factor for ductal closure in human beings is supported by the results of the present experiments in animals.

ACKNOWLEDGEMENTS

My sincere thanks are due to

Professor John Lind Head of the Department of Paediatrics, Karolinska Institutet, for introducing me into the field of neonatal physiology. His personal interest in my work and his extensive knowledge in this field have been of the utmost value.

Professor Ture Petré, former Head of the Department of Anatomy, Karolinska Institutet, who taught me gross anatomy for his interest in my work.

Associate Professor K. Sune Larsson responsible for the Swedish Medical Research Council's Teratology Research Unit, Karolinska Institutet, for his never-failing interest in the problems arising during this study for fruitful discussions and valuable help during the course of the investigations. His optimistic and enthusiastic attitude has been an unceasing source of inspiration. I wish to offer him my warm thanks for giving me the privilege of being a member of his research group.

Associate Professors Allan Beudolf, Department of Anatomy, University of Michigan, Harry Bostrom, Medical Department III, St. Erik's Hospital, Karolinska Institutet and Lars Gyllenstein, Department of Histology, Karolinska Institutet for critical reading of the manuscripts.

Associate Professor Ulf Friberg, Department of Histology, Karolinska Institutet, for stimulating collaboration in one investigation and valuable discussions of others.

Associate Professor Rune Cederlof, Department of Environmental Hygiene, National Institute of Public Health, Stockholm, for advice on statistical methods.

Mrs Margareta Eriksson and Lars Mark and other colleagues for stimulating discussions and technical assistance.

Professor Chester A. Swinyard representing the Association for the Aid of Crippled Children, New York, for his personal engagement in this project.

Mrs Ann Britt Dahlberg, Miss Solveig Johansson, Mrs Tolle Palm and Mrs Marie Louise Wästern for typing the manuscripts.

Mrs Margareta Edmark, Mrs Aino Hallberg, Mr Ove Helstrand, Mrs Anne Marie Johansson, Mrs Marianne Kjellberg, Mrs Göta Lundin, Miss E. Löfgren and Mr Rudolf Rudelfelt for skilful technical assistance.

Mrs Erica Odelberg, for rapid and efficient revision of my English.

My wife, May, for her never-failing patience, encouragement and support throughout this work.

This investigation was supported by grants from

The Swedish Medical Research Council Nos 14N 993-02, 03 and 04 and 14P 993-02, 03 and 04 to the Teratology Research Unit, Karolinska Institutet, and

The Association for the Aid of Crippled Children, New York, as part of its international support for research on foetal growth and development.

Additional financial support has been received from Expressens Fund for Prenatal Research, Stockholm.

Grants to Dr Ulf Friberg from the King Gustaf V 80th Birthday Fund and Knut and Alice Wallenberg Foundation.

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ACTA
PÆDIATRICA
SCANDINAVICA

SUPPLEMENT 189 1969

ON THE ENDOGENOUS
FORMATION OF CARBON
MONOXIDE IN FULL-TERM
NEWBORN INFANTS

BY S. P. FÄLLSTRÖM

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 189 1969

FROM THE DEPARTMENTS OF PEDIATRICS AND CLINICAL PHYSIOLOGY
UNIVERSITY OF GÖTEBORG, S. EDEN

On the endogenous formation of carbon
monoxide in full term newborn infants

BY

S. P. FÄLLSTRÖM

GÖTEBORG 1969

This survey is based mainly on the following five communications, which will be referred to in the text by their Roman numerals, I-V

- I Bjure, J and Fällström S P Endogenous formation of carbon monoxide in newborn infants. I Non-icteric and icteric infants without blood group incompatibility *Acta Paediat Scand* 52 361 1963
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- III Fällström, S P and Bjure, J Endogenous formation of carbon monoxide in newborn infants III ABO incompatibility *Acta Paediat Scand* 57 137 1968
- IV Fällström, S P Endogenous formation of carbon monoxide in newborn infants IV On the relation between the blood carboxyhaemoglobin concentration and the pulmonary elimination of carbon monoxide. *Acta Paediat Scand* 57 321 1968
- V Fällström, S P Endogenous formation of carbon monoxide in newborn infants. V On the relation between the carboxyhaemoglobin concentration and the haemoglobin catabolism calculated from simultaneous determinations of carbon monoxide elimination and total haemoglobin. *Acta Paediat Scand* 57 487 1968.

Included in this survey are the results of determinations of the carbon monoxide (CO) content in room air from the Children's hospital and the Obstetric Department Sahlgren's Hospital, Göteborg, as well as the results of investigations into the methods used, which have not been presented earlier

A presentation in tabular form of the individual results can be obtained by request, from the author

Supported by grants from the Faculty of Medicine, University of Göteborg, the Majblomman Foundation and the Association for the Aid of Crippled Children

The statistical analyses were performed in cooperation with fil lic. Esbjörn Carlström and fil kand Bo Eriksson

The English text was revised by Roy Cooke M D

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INTRODUCTION

At the end of the nineteenth century it was shown that the blood contains small amounts of a combustible gas [27], and it was soon found that this gas was probably carbon monoxide [47]. Since the gas was found in the blood in the absence of known exposure to CO the possibility of an endogenous production of CO was considered.

However it was not until the middle of this century that convincing proofs for an endogenous CO production were presented. In 1949 Sjöstrand reported the finding of increased levels of carboxyhaemoglobin (COHb) in patients with haemolytic diseases [63]. The COHb was determined from the alveolar CO tension, which did not decrease after breathing CO-free air for several hours. Sjöstrand also demonstrated that the expired air always contains higher CO concentration than the inspired air and that this difference increases in haemolytic conditions [63-64]. In a series of papers he showed that CO is formed during the degradation of haemoglobin in an amount corresponding to the formation of four molecules of CO for each molecule of haemoglobin [65, 66, 68]. This finding is in accordance with the theory for haemoglobin degradation, assuming oxidation of the α -methylene carbon atom to carbon monoxide during the splitting of the porphyrin ring [26, 45]. During recent years Sjöstrand's results have been confirmed by Coburn and co-workers, using a technique virtually excluding the influence of exogenous CO [11-13].

Sjöstrand calculated that the amount of CO eliminated by the lungs in healthy adults is accounted for by the normal decay of circulating erythrocytes [65]. On the other hand Coburn *et al.* found in healthy adults as well as in patients with haemolytic diseases, that greater

amounts of carbon monoxide were produced than could be explained on the basis of destruction of circulating erythrocytes alone [11-14]. Other investigations also indicate that additional sources for the endogenous CO production must be considered.

After the administration of ^3H - or ^{14}C -glycine, labelled bilirubin rapidly appears in plasma and bile, and within a few days labelled stercobilin can be demonstrated in faeces [25, 42, 78]. After about 120 days there is a "late peak" of labelled stercobilin in faeces, corresponding to the destruction of aged red cells. The early labelled bilirubin which has been estimated to be 10-20 per cent of the total bilirubin production in normal man [25-42] increases in situations with stimulated erythropoiesis [2]. It has therefore been assumed to depend on the bone marrow activity and possible sources are haemoglobin or haemoglobin precursors in the marrow or circulating red cells with very short life span [52]. Part of this bilirubin is not associated with erythropoiesis but is probably derived from non-haemoglobin haemoproteins in the liver [78]. The formation of early labelled bilirubin is accompanied by CO formation [73, 74-75], which thus constitutes a significant part of the endogenous CO production. Carbon monoxide is also formed during the degradation of myoglobin [67]. The myoglobin mass is however small compared with that of haemoglobin, and the turnover rate of its haeme is slow [70]. Its contribution to the endogenous CO production therefore can be assumed to be slight. From the available information it can be concluded that the endogenous CO production mainly depends on the degradation of haemoglobin, most of which is derived from circulating erythrocytes.

As mentioned above CO is continuously eliminated in the expired air. It has also been shown that oxidation of CO to CO_2 occurs *in vivo* [9-43]. Loumanmaki estimated the mean

In the following presentation COHb is expressed as CO saturation of the haemoglobin in per cent.

compensation would imply that CO elimination could be achieved at a constant CO tension gradient, irrespective of the total amount of haemoglobin.

Sjöstrand reported a positive correlation between the total amount of haemoglobin and the COHb level in healthy children and adults [63]. Hallberg could verify this finding in adult females but not in males [31]. Engstedt, calculating the rate of erythrocyte destruction from COHb, accounted for the total haemoglobin [18]. However available information does not permit a definite conclusion about the influence of the total haemoglobin *per se* on the COHb level.

Following Sjöstrand's report on the finding of increased COHb levels in haemolytic diseases, several clinical investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions [14 18, 29 31 51]. Although the COHb level is only an indirect measure of the endogenous CO formation and theoretical objections can be raised against its use as an index of haemolysis, increased COHb levels have been found in the majority of patients with haemolytic disease compared with healthy adults. Furthermore, a significant correlation has been obtained between COHb and the rate of haemolysis as judged from red cell survival studies [14 18].

THE AIM OF THE PRESENT INVESTIGATION

Haemolytic diseases are frequent during the newborn period and an estimation of the degree of haemolysis is essential for their management. Furthermore, hyperbilirubinaemia is very common at this age in infants without demonstrable haemolytic disease. Information about the rate of haemoglobin catabolism is of great interest for the evaluation of the pathogenesis of the jaundice. Determination of the red cell survival is often not practicable in these

infants and does not always give a true picture of the haemoglobin catabolism. An investigation of the endogenous CO formation therefore seemed to be an interesting approach to the problems of neonatal haemolytic disease and jaundice. Direct estimation of the endogenous CO production is technically difficult in small infants. Determination of the blood COHb level on the other hand can be done comparatively easily and is therefore applicable in clinical practice.

The main purpose of the present investigation was to evaluate the COHb level as an index of haemolysis during the newborn period. Part of the study was therefore devoted to some factors other than haemolysis known to influence the COHb level in blood.

The effect of exogenous CO on infants in the Children's hospital and in the Obstetric Department, Sahlgren's Hospital has been estimated from systematic determinations of the room air CO concentration.

The efficiency of the CO elimination in newborns was estimated from simultaneous determinations of the COHb level and the pulmonary CO elimination (IV).

The relation between COHb and the rate of haemolysis expressed as CO production per g haemoglobin was determined (V) and the influence of the venous haemoglobin concentration on this relation has been evaluated.

In order to establish the association between COHb and haemolysis in a clinical material the COHb level in Rh haemolytic disease, a clinically and serologically well-defined haemolytic process, was determined and related to the severity of the disease (II).

On the assumption that COHb reflects haemoglobin catabolism the COHb level was used to evaluate the contribution of increased bilirubin production to the jaundice in xerotic newborns without blood group incompatibility (I, III).

In order to obtain information on the frequency of increased haemolysis in infants of ABO heterospecific pregnancies the COHb level was determined in infants with obvious

fractional oxidation rate in dogs to be 0.30 per cent of the body CO pool per hour and in two human males to 0.11 and 0.16 per cent per hour respectively [43]. These figures indicate that at physiological COHb levels oxidation of CO is of minor importance. No other way to eliminate CO has been demonstrated [10]. In a steady state the CO produced in the body is thus eliminated almost quantitatively in the expired air.

The solubility coefficient of CO in water is extremely low [32]. In the body CO therefore exists exclusively bound to haemoproteins, mainly to haemoglobin and myoglobin. Each molecule of haemoglobin can bind four molecules of CO corresponding to a CO capacity of 1.34 ml per g haemoglobin.

There are two principle determinants of the COHb level in blood, the CO concentration in inspired air and the rate of formation and elimination of endogenous CO. Blood COHb can be regarded as composed of one exogenous part (COHb_{ex}) and one endogenous (COHb_{end}).

$$\text{COHb} = \text{COHb}_{\text{ex}} + \text{COHb}_{\text{end}} \quad (1)$$

Exogenous CO will influence the COHb level according to the Haldane equation

$$\frac{\text{COHb}}{\text{O}_2\text{Hb}} = M \times \frac{P_{\text{CO}}}{P_{\text{CO}_2}} \quad (2)$$

P_{CO} = CO tension in inspired air in mm Hg

P_{CO_2} = mean pulmonary capillary oxygen tension in mm Hg

O_2Hb = mean pulmonary capillary oxygen saturation in per cent

M = equilibrium constant with the numerical value of 200–250

Several investigators have considered the effect of inspiring high CO concentrations on the COHb level in blood [53] but reports on the influence of CO concentrations in air in the normal range are sparse. Coburn *et al* estimated that in hospital wards (Philadelphia) room air CO was responsible for 0.40 per cent COHb or about half the normal mean level [12]. In non-smoking Navy divers (Bethesda)

the COHb level decreased from 0.88 ± 0.21 per cent to 0.75 ± 0.11 per cent after breathing air with a low and constant CO concentration for several days [15]. The influence of exogenous CO must vary considerably in different situations and may for instance in smokers, greatly surpass that of the endogenous CO production.

If obvious exposure to CO is avoided, the COHb level will to a high degree be determined by the formation and elimination of endogenous CO. After injection of haemoglobin or damaged erythrocytes the CO production and the alveolar CO concentration rapidly increase [13, 68]. The COHb level can therefore be assumed to reflect an increased rate of haemolysis almost instantly. There are reasons to believe that the elimination of CO is determined by the same factors that influence the CO transfer from alveolar air to pulmonary capillary blood. The main factors influencing the gas transfer are assumed to be the alveolar ventilation, pulmonary blood flow, haemoglobin concentration, blood pressures in the pulmonary circulation, mean pulmonary capillary oxygen tension and the CO tension gradient [4, 5, 19]. Because of the time constant for the equilibrium a change in any of these variables of short duration will not alter the COHb level appreciably but their effect is mainly an expression of the mean levels for periods of several hours.

Since the endogenous CO production depends mainly on the degradation of circulating haemoglobin, it is related to the total amount of haemoglobin. Thus a large haemoglobin mass implies a large CO production, even at a normal rate of haemolysis. The haemoglobin mass is correlated to the body size and variations in CO production depending on this factor should be compensated for by variations in respiratory minute volume and diffusing capacity. The haemoglobin concentration, the other determinant of the haemoglobin mass, also influences the gas transfer between blood and alveoli. The pertinent question is to what extent the large CO production of a large haemoglobin mass is compensated for by a more efficient CO elimination. An efficient

compensation would imply that CO elimination could be achieved at a constant CO tension gradient, irrespective of the total amount of haemoglobin.

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The efficiency of the CO elimination in newborns was estimated from simultaneous determinations of the COHb level and the pulmonary CO elimination (IV).

The relation between COHb and the rate of haemolysis expressed as CO production per g haemoglobin was determined (V) and the influence of the venous haemoglobin concentration on this relation has been evaluated.

In order to establish the association between COHb and haemolysis in a clinical material the COHb level in Rh haemolytic disease, a clinically and serologically well-defined haemolytic process, was determined and related to the severity of the disease (II).

On the assumption that COHb reflects haemoglobin catabolism the COHb level was used to evaluate the contribution of increased bilirubin production to the jaundice in icteric newborns without blood group incompatibility (I, III).

In order to obtain information on the frequency of increased haemolysis in infants of ABO heterospecific pregnancies the COHb level was determined in infants with obvious

signs of haemolytic disease as well as in infants without apparent signs of increased haemolysis (III)

MATERIAL

The investigation was restricted to infants with a birth weight above 2500 g. In the majority of the infants the endogenous CO formation was estimated from the COHb level in blood and therefore these infants were selected in a way that the influence of other factors on the COHb level was reduced.

The following groups of newborn infants were studied

Group 1 Seventy-seven healthy newborns without jaundice at repeated examinations (II III) The bilirubin concentration, measured in 39 of the infants, was below 10 mg per 100 ml Blood group incompatibility between infant and mother was excluded One COHb value from each of 75 infants constitute the basis for calculation of normal mean values and standard deviations after birth. In twelve of the infants the COHb level in cord blood was also determined

The original normal material comprised 35 infants (I) Six of these infants were later excluded because of divinylether anaesthesia or instrumental delivery The material was supplemented with 33 infants from group no 5 together with 15 other infants without jaundice

Group 2 Fifty nine infants with Rh haemolytic disease (II)

Group 3 Sixty-two infants selected because of jaundice associated with ABO incompatibility (III) Rh isoimmunization was excluded in all cases

Group 4 Forty six infants of ABO hetero-specific pregnancies selected without regard to the degree of bilirubinaemia (III)

Group 5 Sixty-one infants of ABO homo-specific pregnancies also selected without regard to the degree of bilirubinaemia (III)

Group 6 Forty-six infants with jaundice but no blood group incompatibility or other

signs of haemolytic disease (III) Twenty-nine of these infants were included in the first report (I).

All infants in group nos 1-6 fulfilled the following criteria None of the mothers was smoker No COHb values from cord blood or from the first day of life were included if volatile anaesthetics such as divinylether or trichl. ethylene had been given to the mothers during the delivery Infants delivered by means of Caesarean section or instrumental delivery were not included in the study A few mothers had preeclampsia but no other serious maternal diseases were present. Severe haemorrhage did not occur during the pregnancy or labour

In the majority of cases the mother received 10 mg and the infant 1 mg of vitamin K₂ None of the infants received more than 5 mg.

Signs of asphyxia were not present in the infants with three exceptions. One infant in group no 2 had slight extrauterine asphyxia and in two other infants of that group low fetal heart rate had been registered No infant with clinical signs of respiratory disease was investigated There were no signs of infection or cerebral damage Infants with cephalhaematoma, large cutaneous bruises, melena or other signs of haemorrhage were also excluded from the study No infants were studied after exchange transfusion All infants were in good condition at the time of investigation.

Group 7 Simultaneous determinations of the COHb level and the pulmonary CO elimination were performed on 43 infants (IV) These infants comprised 15 without blood group incompatibility 10 with ABO incompatibility (7 of these were included in group no 3) and 18 infants with Rh haemolytic disease

The infants, to a large extent fulfilled the above mentioned criteria However since the aim of this part of the study was to establish the relation between COHb and CO elimination, the origin of the CO pool was not of primary interest Therefore a few infants were included although their mothers were smokers and some infants were studied after exchange transfusion

In 32 of the infants the total amount of haemoglobin was also determined and the rate of haemolysis was calculated as CO production per g haemoglobin (V). In these infants the influence of exogenous CO was limited to that of the CO in the ambient air

METHODS

The endogenous CO metabolism can be studied in different ways. In a steady state the pulmonary CO elimination equals the endogenous CO formation which thus can be determined from the respiratory minute volume and the difference between the CO concentrations in inspired and expired air. This method has been used by Wranne in newborn infants, but according to him its precision is not very high [76]. Coburn *et al* have developed another procedure which allows the determination of the endogenous CO production independent of exogenous CO and variations in CO elimination by using a rebreathing system and measuring the increase per unit time of the CO saturation in blood and the CO capacity of the body [11]. For precise determination of the COHb increment rebreathing during two or more hours was necessary. Both these methods require the use of breathing systems and are therefore not easily applicable for routine use in small infants.

Determination of the COHb level in blood offers another possibility to study the CO metabolism and under certain prerequisite conditions the COHb gives information about the endogenous CO formation. Sjöstrand opened a new field for haematological research, when he introduced the method for indirect determination of low COHb levels from the alveolar CO tension [61]. Since that time methods have been described allowing direct determination of small amounts of CO in blood with a high precision. They require only small amounts of blood and are thus suitable for use in infants.

Determination of the CO concentration in gas mixtures

The amount of CO in gas mixtures was determined with a Hopcalite Stalex CO-meter according to the method described by Linderholm and Sjöstrand [40]. The procedure used in the present investigation was practically identical with that reported originally.

In the CO-meter CO is oxidized to CO₂ in the presence of the catalyst Hopcalite and the liberated heat is measured by thermistors incorporated in a Wheatstone's bridge. The output from the bridge is registered on a potentiometer writer. Carbon monoxide introduced into the CO-free carrier gas causes a deflection on the potentiometer writer.

If very low CO concentrations in air shall be measured a large gas sample (5-10 l) must be used and the carrier gas must be replaced by the unknown sample. After 5-10 minutes the deflection reaches a plateau, i.e. the heat loss from the measuring cell equals the heat liberated during the combustion of CO. At a constant flow rate through the CO-meter the height of the plateau is proportional to the CO concentration of the gas. The procedure allows the determination of CO concentrations as low as 0.1 part per million (ppm) [40]. High CO concentrations are analyzed by rapid injection of a small volume of the gas sample into the carrier gas. In this case a steady state between heat production and loss is never reached and the deflection takes the appearance of a spike. If the sample is introduced into the carrier gas in less than twenty seconds the height of the deflection is proportional to the amount of CO injected [40]. In this way 0.1 µl CO can be detected by the CO-meter [41].

The response of the Hopcalite CO-meter has been shown to be linear within a wide range of CO concentrations [31-40]. The linearity of the CO-meter used for the present investigations was checked and confirmed for the actual ranges. For the analysis of low CO concentrations in air the sample replaced

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The amount of CO in gas mixtures was determined with a Hopcalite Sialex CO-meter¹ according to the method described by Linderholm and Sjöstrand [40]. The procedure used in the present investigation was practically identical with that reported originally.

In the CO-meter CO is oxidized to CO₂ in the presence of the catalyst Hopcalite and the liberated heat is measured by thermistors incorporated in a Wheatstone's bridge. The output from the bridge is registered on a potentiometer writer. Carbon monoxide introduced into the CO-free carrier gas causes a deflection on the potentiometer writer.

If very low CO concentrations in air shall be measured a large gas sample (5-10 l) must be used and the carrier gas must be replaced by the unknown sample. After 5-10 minutes the deflection reaches a plateau, i.e. the heat loss from the measuring cell equals the heat liberated during the combustion of CO. At a constant flow rate through the CO-meter the height of the plateau is proportional to the CO concentration of the gas. The procedure allows the determination of CO concentrations as low as 0.1 part per million (ppm) [40]. High CO concentrations are analyzed by rapid injection of a small volume of the gas sample into the carrier gas. In this case a steady state between heat production and loss is never reached and the deflection takes the appearance of a spike. If the sample is introduced into the carrier gas in less than twenty seconds the height of the deflection is proportional to the amount of CO injected [40]. In this way 0.1 μ l CO can be detected by the CO-meter [41].

The response of the Hopcalite CO-meter has been shown to be linear within a wide range of CO concentrations [31-40]. The linearity of the CO-meter used for the present investigations was checked and confirmed for the actual ranges. For the analysis of low CO concentrations in air the sample replaced

the carrier gas for a period of three minutes. This length of time was found to be convenient because of the good reproducibility of the deflections and the saving of time and sample gas. The height of the 3 minutes deflection in per cent of the height of the plateau was found to be 83.0 ± 5.4 in the range 0.4–1.5 ppm ($n=7$) and 81.3 ± 4.2 in the range 2.0–2.5 ppm ($n=10$). The relation can thus be assumed to be constant in the actual range.

The sensitivity of the CO-meter varies from time to time and therefore the sample always has to be compared with a calibrating gas analyzed immediately before or after the sample. Calibrating gas¹ with approximately the same CO concentration as the sample was used. The concentration of the calibrating gas was determined through repeated analyses against dilutions of "pure" CO in CO-free air as described by Bjure [4]. The CO concentration was checked regularly during the period of use and was found to be constant. Each new calibrating gas was analyzed against the preceding one and against dilutions. Thus all calibrating gases were thoroughly matched against each other throughout the study.

In the present investigation samples with CO concentration between 0.04 and 0.08 per cent (400–800 ppm) were analyzed with a random error of ± 0.0005 per cent CO (± 5 ppm). Low CO concentrations in the range 0.00005–0.00050 per cent (0.5–5 ppm) were determined with an error of ± 0.000007 per cent CO (± 0.07 ppm).

Determination of the COHb level in blood

The CO content in blood was determined according to Linderholm *et al* and their standard procedure was used [41]. The CO was released from the haemoglobin by 10 per cent sulphuric acid in an extraction chamber and

measured in the Hopcalite CO-meter. The extraction chamber was carefully cleaned with 1 per cent NaOH and distilled water between the analyses. Usually 2 ml of blood was used for the analysis. The COHb level was calculated from the CO content and the haemoglobin concentration using 1.34 ml per g as the CO combining capacity of haemoglobin.

The Hopcalite method is not quite specific for CO and other volatile combustible substances such as acetone, ethanol and ammonia may interfere with the CO analyses. Under normal conditions the amount of interfering gases in the blood is small. The CO-meter is not able to demonstrate any combustible gas in normal plasma [59]. The COHb values found with the Hopcalite method in non-smoking healthy adults agreed well with those reported with the infrared [22] or gaschromatographic method [15]. Sjöstrand's statement that for practical purposes the Hopcalite method can be regarded as specific for CO [59], thus seems to be valid.

There are no reasons to believe that this does not hold true for the newborn infant under physiological conditions. It was found however that volatile anaesthetics such as divinylether given to the mother during the second stage of delivery were associated with the finding of large amounts of combustible gas in the cord blood (Fig. 1). Nitrous oxide also causes deflections on the potentiometer writer but does not seem to pass the placenta in appreciable amounts with the type of intermittent administration used here (1).

The random error of a COHb determination calculated from duplicate determinations was found to be ± 0.047 per cent COHb in the range 0.4–1.0 per cent and ± 0.049 per cent COHb in the range 1.0–4.0 per cent.

The COHb levels in two equivalent groups of full term healthy newborns, aged 4 days and with bilirubin concentrations below 10 mg per 100 ml were determined during the years 1961–63 and 1964–66 respectively. The COHb levels, 0.82 ± 0.15 per cent ($n=14$) and 0.81 ± 0.17 ($n=16$) agreed well indicating a good reproducibility of the method.

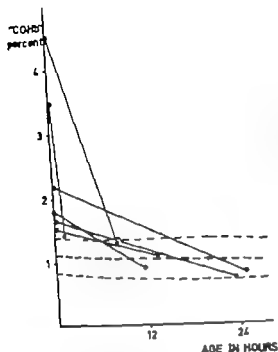


Fig. 1 Measured COHb level in cord blood and on the first day after birth in infants whose mothers received diethyl ether anaesthesia during the second stage of labour

Determination of the pulmonary CO elimination (IV)

An open circuit breathing system was used for the determination of the pulmonary CO elimination with the infant attached by means of a nose mask without valves. The infant breathed room air which was sucked through the mask at a constant flow rate and collected in bags. The CO elimination per unit time (\dot{V}_{CO}) was calculated from the increase of the CO concentration in the air sucked through the system and the volume of the passing air. The Hopcalite CO-meter was used for the CO analysis. Special precautions were necessary to prevent contamination of the collected air with exogenous CO or with other volatile substances combustible in the CO-meter.

Preliminary investigations showed a very low CO elimination when the room air CO concentration was high. This might depend on

a non-steady state, since it was found that the CO elimination was reduced after an increase of the inspired CO concentration (Fig. 2). In order to reduce the effect of variations in inspired CO only investigations with room air CO below 1.5 ppm were included. During the period of study two infants were excluded for this reason. Furthermore, at the time of investigation the infant breathed air which had been collected during 30-60 min prior to the study from the ward.

Duplicate determinations of the CO elimination were done in most cases. The random error of a single determination was calculated from the difference between duplicate determinations to $\pm 0.26 \mu\text{l}$ per min. Wranne estimated the CO elimination in small infants with practically the same error $0.27 \mu\text{l}$ per min using a different procedure for the collection of expired air and another CO-method [76].

Determination of the total amount of haemoglobin (V)

A modification of the open circuit CO-method [54] was used for the determination of total haemoglobin. The same breathing system and nose mask were used as for the determination of the CO elimination. The infant breathed a mixture of CO and air during a period of 10 min. The amount of CO absorbed by the infant was calculated from the volume of air passing through the system and the decrease of the

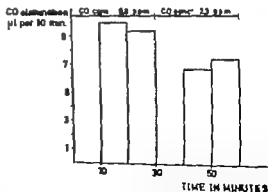


Fig. 2. Pulmonary CO elimination in one infant breathing air with 0.9 and then 2.3 ppm CO

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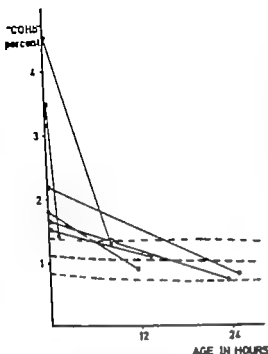


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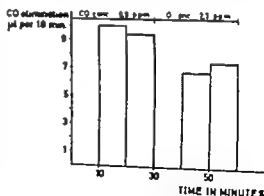


Fig. 2. Pulmonary CO elimination in one infant breathing air with 0.9 and then 2.3 ppm CO.

CO concentration in the gas mixture. The COHb level in blood was measured before and after CO breathing. The total amount of haemoglobin was calculated from the increase of the CO saturation in blood and the amount of CO absorbed using 1.34 ml CO per g as the CO combining capacity of haemoglobin.

The value 1.34 is obtained using 66 400 for the molecular weight of haemoglobin. However this has recently been calculated to be 64 458 [7] corresponding to a CO capacity of 1.39 ml per g haemoglobin. Since the haemoglobin method was standardized with haemoglobin solutions determined by their oxygen capacity the COHb values are not influenced by the value for the haemoglobin molecular weight. The total amount of haemoglobin determined by the CO-method would decrease 3.5 per cent if the factor 1.39 was used.

The distribution of CO in the body is determined by the amounts of different haemoproteins and their relative affinities for CO. The main part of the CO is bound to circulating haemoglobin and equilibrium is reached rapidly in the blood [43]. The extravascular CO pool mainly consists of CO bound to myoglobin. The size of this pool has been estimated from simultaneous determinations of the blood volume by a CO dilution technique and by dilution of isotope labelled red cells to 16 ± 10 per cent in man [49]. Equilibrium between intravascular and extravascular CO pools is reached within 15–45 min in dogs [43]. Sjögstrand estimated that with his rebreathing CO method about 5 per cent of administered CO was bound to extravascular haemoproteins after 15 min rebreathing [62]. In the present procedure the extravascular CO loss was probably of less importance since the CO exposure was shorter and the initial alveolar CO tension lower than in the rebreathing method. Furthermore the relative amount of myoglobin is smaller in newborns than in adults [33].

During the period of CO breathing the circulating erythrocytes can be assumed to pass the pulmonary capillaries several times, which should allow a fairly even distribution of the CO in the blood.

The random error of a single determination

of the total amount of haemoglobin was calculated from duplicate determinations to be ± 5.5 g ($n=10$). This error is comparatively large compared with isotope techniques [6]. The procedure used could however easily be added to a preceding determination of the CO elimination and allowed a rapid estimation of the haemoglobin mass. This was a great advantage in situations when the investigation had to be completed rapidly before an exchange transfusion.

Determination of the serum bilirubin concentration

Total serum bilirubin was determined according to the method of Jendrassik-Cleghorn [34] with the simplified modification described by Jendrassik and Gróf [35]. In the reaction 0.1 ml serum or diluted serum, 0.4 ml caffeine mixture and 0.1 ml Diazo reagent were used. The patient's serum with caffeine mixture and water was used as blank. The extinction was read after 15 min at 530 m μ in a Beckman B spectrophotometer with voltage stabilizer. The method was standardized with dilutions of commercial bilirubin (Merck AG Darmstadt) in serum. Standardization was repeated regularly and the extinction of the bilirubin preparation was found to be very constant. A control serum (Versatol Paediatric) was used on each occasion of analysis. The mean value for these analyses agreed well with the concentration given by the manufacturer. The standard deviation of the determinations of the control sera was 0.3 mg per 100 ml. Each unknown serum was analyzed in duplicate and the random error of a single determination was ± 0.4 mg per 100 ml.

The amount of directly reacting bilirubin was also determined. Except in some cases of Rh haemolytic disease only small amounts were found. Since the total bilirubin is probably the best index of bilirubin production only the values for total bilirubin were used in this presentation.

Determination of the haemoglobin concentration in blood

Haemoglobin was determined as oxyhaemoglobin after addition of sodium carbonate (0.02 ml blood and 3.98 ml 0.1 per cent Na_2CO_3). The extinction was read in a Beckman B spectrophotometer at 540 m μ with water as blank. The method was standardized with haemoglobin solutions determined by means of their oxygen combining capacity. On each occasion of analysis a known haemoglobin solution was included as control. The standard deviation of the extinction for the control solution corresponded to 0.26 g haemoglobin per 100 ml.

The random error of the method determined from the difference between two capillary samples was found to be ± 0.3 g per 100 ml. When duplicate venous samples were analyzed the variation was of the same magnitude as between duplicate capillary samples.

Determination of the number of reticulocytes

The percentage of reticulocytes was counted on a smear after vital staining for at least 20 min with brilliant cresyl blue. One thousand or more erythrocytes were counted with 1000x magnification. The random error of the method was calculated from the difference between two smears from the same patient and was found to be ± 1.5 reticulocytes per 1000 counted cells.

The determinations of the bilirubin and haemoglobin concentrations and the number of reticulocytes were performed in the Department of Clinical Chemistry the Children's hospital.

The blood grouping and serological tests were done with standard techniques in the Blood Bank, Sahlgren Hospital.

RESULTS AND DISCUSSION

PART I. GENERAL ASPECTS ON THE CO METABOLISM IN NEWBORN INFANTS

On the influence of exogenous CO on the COHb level in blood

During pregnancy the CO tension in the maternal blood influences the COHb level in the fetus [24]. A mother who is a smoker may

increase the COHb level of her fetus considerably and this effect will last one or two days after birth. With few exceptions no infants of smoking mothers were included in the present investigation and the influence of exogenous CO after birth was therefore limited to the effect of the CO content in the inspired air. In order to determine the magnitude of this contribution to the COHb level the CO concentration in room air from the Children's hospital was determined systematically during one year. Air was collected between 8 and 10 o'clock in the morning twice a week on randomly chosen days from the ward caring for the newborn infants. During the first months air from one ward in the Obstetric Department, Sahlgren's Hospital, collected on the same days and at the same time in the morning was analyzed. The CO concentration in the Children's hospital was also determined each day during some weeks and repeated determinations were done on some days.

The CO concentrations in room air from the Children's hospital during the period August 1966 to July 1967 are shown in Table I.

Table I CO concentration (ppm) in air from the Children's hospital, Göteborg during the period August 1966 to July 1967. As comparison the results of two earlier investigations are given.

Göteborg Month		mean	S.D.	range
JAN	9	1.08	0.59	0.4-2.5
FEB	8	0.96	0.50	0.3-2.1
MAR	8	1.29	0.92	0.7-3.5
APR	9	0.72	0.18	0.4-1.0
MAY	8	0.69	0.11	0.3-0.8
JUN	9	0.54	0.09	0.4-0.7
JUL	9	0.60	0.26	0.4-1.1
AUG	9	0.66	0.35	0.4-1.5
SEP	9	0.72	0.32	0.4-1.3
OCT	8	1.01	0.42	0.7-1.9
NOV	9	1.28	0.47	0.8-2.1
DEC	8	1.65	0.90	0.5-3.2
TOTAL	103	0.92	0.57	0.4-3.5
Uppsala (Wernae)				0.2-1.5
Philadelphia (Coburn <i>et al.</i>)		2.2	0.98	0.4-4.5

CO concentration in the gas mixture. The COHb level in blood was measured before and after CO breathing. The total amount of haemoglobin was calculated from the increase of the CO saturation in blood and the amount of CO absorbed using 1.34 ml CO per g as the CO combining capacity of haemoglobin.

The value 1.34 is obtained using 66 400 for the molecular weight of haemoglobin. However this has recently been calculated to be 64 458 [7], corresponding to a CO capacity of 1.39 ml per g haemoglobin. Since the haemoglobin method was standardized with haemoglobin solutions determined by their oxygen capacity the COHb values are not influenced by the value for the haemoglobin molecular weight. The total amount of haemoglobin determined by the CO-method would decrease 3.5 per cent, if the factor 1.39 was used.

The distribution of CO in the body is determined by the amounts of different haemoproteins and their relative affinities for CO. The main part of the CO is bound to circulating haemoglobin and equilibrium is reached rapidly in the blood [43]. The extravascular CO pool mainly consists of CO bound to myoglobin. The size of this pool has been estimated from simultaneous determinations of the blood volume by a CO dilution technique and by dilution of isotope labelled red cells to 16 ± 10 per cent in man [49]. Equilibrium between intravascular and extravascular CO pools is reached within 15–45 min in dogs [43]. Sjöstrand estimated that with his rebreathing CO method about 5 per cent of administered CO was bound to extravascular haemoproteins after 15 min rebreathing [62]. In the present procedure the extravascular CO loss was probably of less importance since the CO exposure was shorter and the initial alveolar CO tension lower than in the rebreathing method. Furthermore the relative amount of myoglobin is smaller in newborns than in adults [33].

During the period of CO breathing the circulating erythrocytes can be assumed to pass the pulmonary capillaries several times, which should allow a fairly even distribution of the CO in the blood.

The random error of a single determination

of the total amount of haemoglobin was calculated from duplicate determinations to be ± 5.5 g ($n=10$). This error is comparatively large compared with isotope techniques [6]. The procedure used could, however easily be added to a preceding determination of the CO elimination and allowed a rapid estimation of the haemoglobin mass. This was a great advantage in situations when the investigation had to be completed rapidly before an exchange transfusion.

Determination of the serum bilirubin concentration

Total serum bilirubin was determined according to the method of Jendrassik-Cleghorn [34] with the simplified modification described by Jendrassik and Gróf [35]. In the reaction 0.1 ml serum or diluted serum, 0.4 ml caffeine mixture and 0.1 ml Diazo reagent were used. The patient's serum with caffeine mixture and water was used as blank. The extinction was read after 15 min at 530 m μ in a Beckman B spectrophotometer with voltage stabilizer. The method was standardized with dilutions of commercial bilirubin (Merck AG Darmstadt) in serum. Standardization was repeated regularly and the extinction of the bilirubin preparation was found to be very constant. A control serum (Versatol Paediatric) was used on each occasion of analysis. The mean value for these analyses agreed well with the concentration given by the manufacturer. The standard deviation of the determinations of the control sera was 0.3 mg per 100 ml. Each unknown serum was analyzed in duplicate and the random error of a single determination was ± 0.4 mg per 100 ml.

The amount of directly reacting bilirubin was also determined. Except in some cases of Rh haemolytic disease only small amounts were found. Since the total bilirubin is probably the best index of bilirubin production, only the values for total bilirubin were used in this presentation.

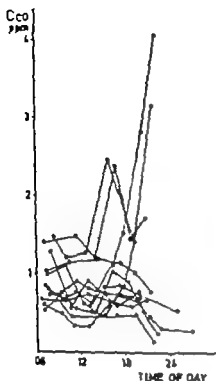


Fig. 4. Variation in room air CO concentration during the same day

actually of the same magnitude as the variation encountered in healthy newborns (I II) and adults (V). The influence of exogenous CO was probably not of that great importance. Because of the time constant for equilibrium between air and blood peak CO concentrations in air of short duration do not increase the CO saturation of blood as much as indicated by Haldane's equation. Furthermore it is possible that these peaks represented a contamination with combustible gases other than CO.

On the relationship between the COHb level in blood and the pulmonary CO elimination (IV)

It can be assumed that in most of the infants the COHb level was determined mainly by the endogenous formation and the elimination of CO. Impaired CO elimination leads to increased COHb levels and it was essential

to investigate this possibility in the newborn infants. In full-term infants without signs of respiratory disease increased COHb levels were always found in connection with an increased pulmonary CO elimination. This was true from the first day after birth and also in the presence of haemolytic disease with anaemia (IV). The positive correlation between COHb and CO elimination in newborns permits the conclusion that the increased COHb levels found in many infants did not depend on an impaired CO elimination in comparison with other newborns.

It was also of interest to evaluate the efficiency of the CO elimination in newborn infants compared with that in adults. The values for the alveolar ventilation and the pulmonary diffusing capacity during the first week of life compare favourably with adult values related to body size (37). They indicate that the pulmonary CO elimination in the newborn should be at least as efficient as that in the adult. This conclusion was supported by the results of determinations of the COHb level in infants after measuring the total amount of haemoglobin with the CO-method. The half time of elimination of the extra CO was 2.5 ± 0.5 hours, which is shorter than in adults (35) (Fig. 5).

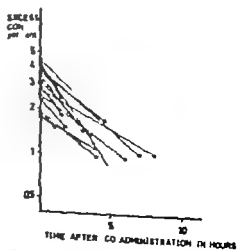


Fig. 5. COHb level in blood after exposure to CO. x —time after exposure, y —difference between the measured and initial COHb levels.

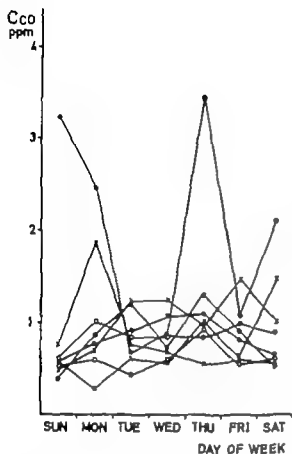


Fig. 3 Variation in room air CO concentration (C_{CO}) during the same week.

The distribution of the values was skew and therefore the standard deviations given in the table cannot be used with certainty for estimation of the confidence intervals. It was estimated from tables of distribution-free tolerance limits [69] that 95 per cent of the CO concentrations could be assumed to fall within the range given for the whole period ($y=0.99$).

A considerable variation was found from day to day during the same week (Fig. 3) and also during the same day a marked variation could be found (Fig. 4).

The room air CO concentration in the Obstetric Department was lower than that in the Children's hospital. Mean values and standard deviations for the determinations in the two hospitals from the same day were 0.78 ± 0.42 ppm (range 0.35–1.99) and 1.07 ± 0.55 ppm (range 0.35–2.46) respectively ($n=31$).

The COHb level corresponding to the CO

concentration in inspired air ($COHb_{ei}$) was calculated from Haldane's equation assuming P_{CO} to be 93 mm Hg and O_2Hb 98 per cent [37] and using the value 210 for the equilibrium constant [58]. The room air CO concentration in the Children's hospital on the average corresponded to 0.15 per cent COHb (range 0.06–0.55 per cent), which constitutes about one fifth of the level found in healthy newborns. Assuming that the relation between the CO concentrations in the Children's hospital and the Obstetric Department was constant during the year the average influence of exogenous CO in the Obstetric Department can be estimated to be 0.10 per cent COHb.

The CO content in hospital air in this city was somewhat higher than that reported from Uppsala [76] but lower than that in Philadelphia [12] (Table 1). The calculated value for COHb should be regarded as an approximate estimation of the influence of the exogenous CO on the COHb. The non-specificity of the Hopcalite CO method is probably of greater importance during the determination of the CO content in the ambient air than in the blood. This implies that the $COHb_{ei}$ might have been overestimated. The accuracy of the estimation also depends on to what extent the determined CO concentrations were representative for the period of study. A large variation could be found within one day but the majority of repeated determinations fell within a comparatively narrow range (Fig. 4). The morning value was therefore assumed to be an acceptable estimate of the mean level for the day. Except for the increase of the traffic outside the hospital there was no change in the local conditions during the period of investigation which could be suspected to influence the degree of air pollution in the wards. The CO concentrations in the Children's hospital during two earlier periods agreed well with those reported here. Although the estimated average influence of the exogenous CO was relatively small the range of this influence was considerable. The variation of the COHb level in blood corresponding to the range of the CO concentrations in air was

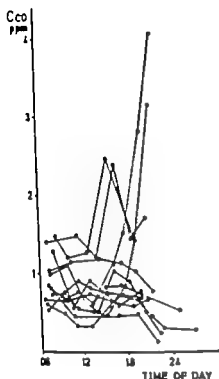


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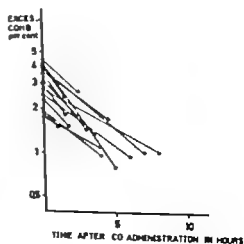


Fig. 5. COHb level in blood after exposure to CO. Δ = time after exposure, Δ = difference between the measured and initial COHb levels.

Coburn *et al* also found a correlation between the COHb level and the CO production in adults with haemolytic disease [12]. The random error of an estimate of the endogenous CO formation from the COHb level was however large, ± 0.80 ml CO per hour corresponding to ± 46 per cent of the mean. According to Coburn *et al* the variation in the relation between COHb and CO production could not be explained by the errors of the methods employed but could be attributed to the influence of variations in the alveolar ventilation and pulmonary diffusing capacity. They concluded that COHb is of limited value as a predictor of the endogenous CO formation in the individual case.

The correlation between the COHb level and the pulmonary CO elimination in newborn infants was good ($r=0.90$). The random error of an estimate of the CO elimination from the COHb was $\pm 4.0 \mu\text{l}$ per 10 min, or ± 33 per cent of the mean. About one fourth of this variation could be explained by the error in the determination of CO elimination. If the COHb level was related to the CO elimination per kg body weight the correlation coefficient was 0.91 and the error of an estimation of the CO elimination ± 25 per cent (Fig. 6). In a steady state the pulmonary CO elimination approximately equals the endogenous CO formation. In this situation the COHb level should be a fairly good predictor of the CO production in the body.

Coburn *et al* did not take the body size into consideration in their calculations [12]. They do not give the weight of their patients, but the reported values for total haemoglobin and venous haemoglobin concentration indicate a large variation in the blood volume (3.5–6.9 l) which should imply a large variation in the body size. It is possible that this factor caused part of the large variation in the relation between COHb and CO production which they found. In a later communication data were presented allowing calculation of CO production per kg [14]. These values have been plotted in Fig. 6 and their relation to the

COHb level agreed well with that found in newborns.

On the relationship between the COHb level and the rate of haemolysis (II V)

If exposure to CO can be avoided and the pulmonary function is normal the COHb level in blood will reflect the endogenous CO formation. The association between increased COHb levels and increased haemolysis has repeatedly been demonstrated in adults [14, 18, 29, 51, 63] and also in isolated investigations on newborns [1, 50]. This finding was verified by the present investigation which showed markedly increased COHb levels in Rh haemolytic disease of the newborn (II). The COHb level was significantly correlated to the severity of the disease. Thus in 17 of 21 infants with COHb levels exceeding the normal mean level by more than 2 S.D. during the first hours after birth the bilirubin concentration increased by more than 0.5 mg per 100 ml per hour. In infants with lower COHb the rate of bilirubin increase was slower. This indicates that there is a close association between COHb and the rate of haemolysis.

A significant correlation was found between the COHb level and the CO elimination per g haemoglobin ($r=0.69$), which can be assumed to reflect the rate of haemolysis (V). The random error of an estimate of the rate of haemolysis from COHb was however considerable, ± 48 per cent of the mean. This variation was partly explained by the large errors in the determination of the CO elimination and total haemoglobin but must be considered when the COHb levels are evaluated. A comparison with earlier investigations on adults [12, 14, 18] showed a good agreement between the investigations with approximately the same degree of correlation between the two variables. The comparison suggested a curvilinear regression of COHb upon the rate of haemolysis. The combined results were found to fit best an equation of the type $y=a+bx^4$. The equation calculated from the results of the present

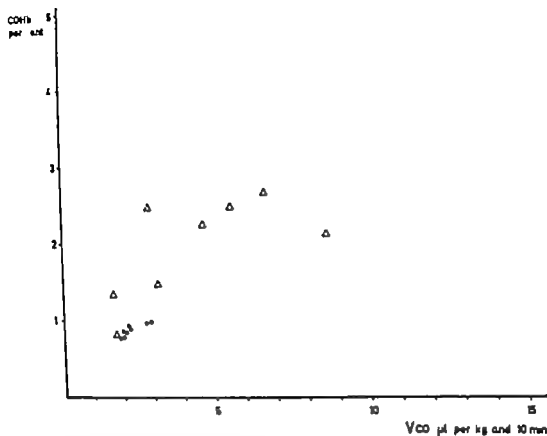


Fig. 6. The relationship between CO elimination per kg (x) and COHb (y). Open circles infants with probable exposure to CO. Filled circles infants with no exposure to CO. Triangles adults (calculated from Coburn *et al* 1966). Regression equation for the infants $y = 0.30x - 0.25$ (0.91).

investigation was described by $y = 0.31 + 1.71x$ (x = CO elimination in μ l per g haemoglobin per 10 min, y = COHb in per cent). However further investigations are necessary to establish the relationship between the two variables.

Coburn *et al* have derived equations describing the major physiological variables determining the COHb level in blood under steady state conditions and the change of COHb when any of the several variables are suddenly altered [12]. The following equation is assumed to describe the steady state

$$\text{COHb} = \frac{V_{\text{CO}} M (\text{O}_2 \text{Hb})}{P_{\text{CO}_2}} \times \left[\frac{1}{D_L} + \frac{P - P_{\text{CO}_2}}{V} \right] \quad (3)$$

V_{CO} = rate of endogenous CO formation in ml STPD per min

M = equilibrium constant in Haldane's equation

$\text{O}_2 \text{Hb}$ = mean pulmonary capillary oxygen saturation in per cent

P_{CO_2} = mean pulmonary capillary oxygen tension in mm Hg

D_L = pulmonary diffusing capacity for CO
in ml STPD per min per mm Hg

P_B = barometric pressure

P_{H_2O} = vapor pressure of water at 37 C

V_A = alveolar ventilation in ml STPD per min

Since the rate of haemolysis is expressed by the CO production/total haemoglobin ratio the following equation for the relation between COHb and haemolysis can be derived

$$\text{COHb} = \frac{V_{CO}}{\text{THb}} \times \frac{M(\text{O}_2\text{Hb})}{P_{\text{CO}_2}} \times \left[\frac{\text{THb}}{D_L} + \frac{\text{THb}(P_B - P_{H_2O})}{V_A} \right] \quad (4)$$

THb = total amount of haemoglobin in g

In the absence of cardiopulmonary disease

$\frac{M(\text{O}_2\text{Hb})}{P_{\text{CO}_2}}$ can be assumed to be constant

THb is a function of the blood volume and the haemoglobin concentration. The equation can therefore be written

$$\text{COHb} = K_1 \times \frac{V_{CO}}{\text{THb}} \times \text{Hb} \times \left[\frac{10\text{BV}}{D_L} + \frac{10\text{BV}(P_B - P_{H_2O})}{V_A} \right] \quad (5)$$

Hb = venous haemoglobin concentration in g per 100 ml

BV = blood volume in l

The numerical value of the constant K_1 is to some degree dependent on the haemoglobin concentration

BV, V_A and D_L are all related to the body size. This will reduce the influence of the body size on the terms within the brackets. If these terms are regarded as a constant, equation (5) can be simplified to

$$\text{COHb}_{\text{rel}} = K_2 \times \frac{V_{CO}}{\text{THb}} \times \text{Hb} \quad \text{or} \quad (6)$$

$$\frac{\text{COHb}_{\text{rel}}}{\text{Hb}} = K_2 \times \frac{V_{CO}}{\text{THb}} \quad (7)$$

BV is well correlated to the body weight, while the relationship between V_A or D_L and body size changes with the age of the individual. The value of the constant K_2 therefore varies with age.

If V_{CO} is expressed in μl per 10 min, the constant in equation (7) can be calculated to be 0.133 assuming $M=210$, $\text{O}_2\text{Hb}=98$ per cent, $P_{\text{CO}_2}=93$ mm Hg, $D_L=2.1$ ml per mm Hg per min, $V_A=440$ ml per min, $\text{BV}=90$ ml per kg, the body weight = 3.5 kg, and the body/venous haematocrit ratio = 0.91 [6, 37, 58].

The relation between $\frac{V_{CO}}{\text{THb}}$ (x) and $\frac{\text{COHb}}{\text{Hb}}$ (y) calculated from the results of the present investigation (V) was described by $y = 0.144x + 0.028$ with $r=0.73$ and the random error of an estimate of haemolysis ± 46 per cent. The blood volume in infants with Rh haemolytic disease 65 ml per kg (V), was much lower than in the other groups. If the infants with Rh haemolytic disease were excluded the observed equation was $y = 0.146x + 0.025$ $r=0.89$ and the error of an estimate of haemolysis ± 33 per cent. The value of the constant in equation (7) for $\text{BV}=65$ ml per kg was calculated to be 0.096. The observed equation for the infants with Rh haemolytic disease was $y = 0.102x + 0.049$ with $r=0.39$ and the error of an estimate of haemolysis ± 37 per cent. The calculated and the observed values of the constant K_2 thus agreed well. The effect of the blood volume on the numerical value of this constant was clearly demonstrated in the present material. The low blood volume in Rh haemolytic disease partly depended on an early clamping of the cord but was also an effect of the anaemia. The haemoglobin concentration also influenced the size of the constant through its effect on the pulmonary diffusing capacity but this effect was probably of less importance.

According to equation (7) the COHb level is directly proportional to the rate of haemolysis at a constant haemoglobin concentration. In the case of anaemia the rate of haemolysis is

underestimated by the COHb level. This influence of the haemoglobin concentration on the relation between COHb and haemolysis was in accordance with the suggested curvilinear relation between the two variables (IV).

From equation (7) also follows that the COHb level is related to the CO production per kg body weight, which was verified by the results of the present investigation (IV).

PART II. CLINICAL ASPECTS ON THE ENDOGENOUS CO METABOLISM IN NEWBORN INFANTS

On the endogenous CO formation in full-term healthy newborns (I II III V)

In full-term healthy newborns without jaundice (measured bilirubin concentration below 10 mg per 100 ml) increased COHb levels were found during the first week after birth compared with adult values (Table 2) (I II). The highest COHb values were found in cord blood with a decreasing level during the first 12-24 hours. On the second and third day the COHb level was constant and after this a further decrease towards adult values was seen.

The high COHb level found in cord blood might be explained by an inefficient CO elimination through the placenta or by the effect of the low oxygen tension and pH prevailing at birth on the equilibrium between the CO tension and COHb [37]. Consequently the decreasing COHb level during the first day

should depend on a new equilibrium established after birth. Wranne found that more CO was eliminated in the expired air during the first day than on the following days [77]. He estimated that the excess of CO eliminated on the first day was not entirely accounted for by the decrease of the CO pool and suggested that it also reflected the destruction of a population of erythrocytes with increased fragility immediately after birth [60].

The pulmonary CO elimination in newborn infants compared favourably with that in adults from the first day after birth (IV). There is therefore no reason to believe that after the first day the increased COHb level in healthy newborns was an effect of CO retention. Simultaneous determinations of the CO elimination and total haemoglobin in six infants aged 73-127 hours and with bilirubin concentration below 10 mg per 100 ml (case nos 7 V) showed that the CO elimination corresponded to the degradation of 1.5 per cent of the haemoglobin mass per day. Wranne came to the same figure in his estimation of the daily haemoglobin catabolism [77]. These findings were in accordance with the results of earlier estimations of the red cell survival in newborn infants, which have practically all demonstrated a shortened life span of the fetal red cells [23-79].

A uniformly reduced red cell survival cannot explain the reduction of the fractional haemoglobin catabolism, suggested by the decreasing COHb level after the third day of life. In a longitudinal investigation during the first week after birth Koch was not able to demonstrate any changes of importance in ventilation, diffusing capacity, oxygen tensions or acid-base balance after the first day [37]. It seems therefore unlikely that the decreasing COHb level after the third day should depend on a change of the equilibrium between the CO in the blood and the alveoli. The possibility of a population of fragile red cells disappearing rapidly during the first day(s) has already been mentioned. Other sources for the CO production than circulating erythrocytes must also be considered.

Table 2 COHb level in full-term healthy newborns during the first week compared with that in healthy non-smoking adults

Age		mean	S.D.
Cord blood	12	1.12	0.14
1-12 hr	13	1.05	0.15
13-24 hr	8	1.02	0.18
25-48 hr	12	0.92	0.13
49-72 hr	14	0.93	0.11
73-96 hr	17	0.77	0.13
97-144 hr	11	0.76	0.10
Adults	11	0.72	0.09

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Vest has shown that the early peak of labelled bilirubin after administration of ^{15}N glycine is large in newborn infants [71]. The formation of early labelled bilirubin is to a large extent dependent on the erythropoietic activity. A very lively erythropoiesis is found during the last period of intrauterine life and continues during the first days after birth [36]. After about three days the erythropoietic activity in the marrow suddenly decreases, manifested by a drop in the reticulocyte count [57]. These changes coincide with the decrease of the COHb level found in this investigation. Thus it is possible that the increased COHb level during the first days partly reflected an increased CO formation associated with the erythropoiesis.

On the endogenous CO formation in icteric newborns without blood group incompatibility (I III IV V)

In full term newborn infants with jaundice not caused by blood group incompatibility increased COHb level (I III) and increased CO elimination (IV) were found in comparison with non icteric infants. In 33 infants with bilirubin concentration 19.3 ± 8.1 mg per 100 ml (range 6.0–35.2) on the fourth–sixth day after birth the COHb level was 10.2 ± 0.25 per cent (mean \pm S.D.). Both the COHb level and the CO elimination were significantly correlated to the bilirubin concentration ($r=0.76$ and 0.73 respectively). In five infants (case nos 8–12, V) with bilirubin concentration 10.9 – 27.8 mg per 100 ml (mean 16.6) simultaneous determinations of the CO elimination and total haemoglobin showed an average CO elimination corresponding to the destruction of 2.4 per cent of the haemoglobin mass per day. These findings indicate that an increased bilirubin production contributed to the hyperbilirubinaemia in this group of infants.

Practically all newborns have increased serum bilirubin concentrations compared with adults and visible jaundice is very common. The problem of neonatal jaundice has been exten-

sively reviewed in several monographs [8, 39–56]. In the fifties the nature of the bilirubin pigments was clarified in more detail and evidence was presented for a deficient hepatic conjugation and excretion of bilirubin in newborn infants [8–56]. This mechanism is generally accepted as the common denominator of neonatal jaundice and is assumed entirely to account for the hyperbilirubinaemia in many infants.

In most cases the jaundice appears on the second or third day after birth, reaches its maximum within a further two or three days and then subsides. There are many factors which influence the course and intensity of the hyperbilirubinaemia and by experience certain criteria have been established indicating the existence of such factors in the individual case. Jaundice observed on the first day is often explained by a haemolytic disease. If the bilirubin concentration reaches a high level, an underlying disease is often suspected, but there is considerable uncertainty about which level should be regarded as pathological.

In the present group of icteric newborns the clinical course was of no concern except that the bilirubin concentration in some infants reached a high level. Blood group incompatibility was excluded in the selection of infants as well as some other factors known to predispose the infant to hyperbilirubinaemia such as maternal diabetes, immaturity, anoxia and melena [39–46, 56]. The small amounts of vitamin K given to the infants should not interfere with the red cell metabolism [79]. None of the infants displayed signs of infection. Asymptomatic infections have been found in infants with increased bilirubinaemia [16], and this possibility was not excluded systematically. Routine haematological investigation did not suggest a haemolytic disease, but no comprehensive investigation was done to diagnose other haemolytic diseases than those caused by iso-immunization.

However it is not likely that an increased bilirubin production in the present group was caused by specific haemolytic diseases,

and an alternative explanation of the hyperbilirubinaemia seems more attractive. In the previous section it was mentioned that increased haemoglobin catabolism was a regular finding in healthy newborns. In some infants this physiologic process might be exaggerated leading to a marked hyperbilirubinaemia. The fact that the same relation between the COHb level and the bilirubin concentration was found at different bilirubin levels (III) speaks in favour of this hypothesis. One has not been able to find a correlation between the red cell survival and the bilirubin level in newborn infants [72]. It is therefore possible that neonatal jaundice is caused partly by "abundant bilirubin," that is bilirubin formation associated with the erythropoiesis or with the degradation of other haemoproteins than haemoglobin.

On the endogenous CO formation in Rh haemolytic disease of the newborn (II IV V)

In Rh haemolytic disease of the newborn very high COHb levels were often found (II). If the bilirubin or haemoglobin concentration at birth necessitated exchange transfusion, the COHb level during the first 12 hours was found to be 2.04 ± 0.96 per cent (range 0.7%–5.0% per cent). In other haemolytic conditions, in the absence of exposure to CO, the COHb values in the upper range are rare. According to the equation given above, the mean value corresponded to more than a tenfold increase of erythrocyte destruction (V), which was in agreement with the results of earlier red cell survival studies in this disease [44]. In 22 of the 26 infants requiring exchange transfusion on the first day after birth the COHb level exceeded the normal mean level by more than two SD. In the four infants with low COHb the rate of bilirubin increase was comparatively slow less than 0.5 mg per 100 ml per hour.

The COHb values in cord blood were lower and often fell within the normal range even if the infant demonstrated definite signs of haemolytic disease (II). In infants followed by repeated COHb determinations the COHb

level was found to increase significantly after birth. There was a significant correlation between the COHb level and the pulmonary CO elimination in Rh haemolytic disease on the first day ($r=0.94$) as well as on the following days ($r=0.68$) (IV). Practically the same relationship was found between the two variables in these infants as in other groups of full-term newborns. This indicates an efficient CO elimination in Rh haemolytic disease and it is unlikely that the increasing COHb level after birth was an effect of CO retention. There seems to be no other explanation for the increasing COHb than an accelerated CO production. At birth there is a far-reaching adjustment of the circulation to extrauterine life with for instance an improved blood flow through the liver. This may imply an increased removal and destruction of the sensitized red cells, explaining a rising CO production.

Infants fulfilling the serological criteria for Rh haemolytic disease but with haemoglobin and bilirubin concentrations at birth not requiring exchange transfusion had normal or slightly increased COHb levels during the first day. After the first day however definitely increased COHb values were found in most of these infants (range 0.49–2.24 per cent). Several infants demonstrated an increasing COHb level at repeated analyses. Although there was a significant correlation between the COHb and the bilirubin concentration ($r=0.65$), increased COHb values without marked hyperbilirubinaemia were found in some infants indicating a compensated haemolysis.

The COHb level in Rh haemolytic disease was significantly correlated to the variables generally used to evaluate the severity of the disease, such as the bilirubin concentration, haemoglobin concentration and the number of reticulocytes. In medical practice the relation between the COHb level and the rate of bilirubin increase is of special interest, since it is essential to evaluate the risk of kernicterus in every case of haemolytic disease of the newborn. If the COHb level exceeded the normal mean

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In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r=0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4-6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the hyperbilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease, and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of

circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism, irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al.* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al.* The influence of exogenous CO is of particular importance since it may be extremely variable and may

level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants. A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days. After the first day the association between the COHb and the rate of bilirubin increase was less marked.

Rh haemolytic disease was the only group investigated in which significant anaemia occurred. It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis in this group. The bilirubin production is however also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase.

On the endogenous CO formation in infants of ABO heterospecific pregnancies (III IV V)

About one fifth of all pregnancies are ABO heterospecific, that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells. In many cases anti A and/or anti B with "immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20, 38]. The ABO antigens are usually well developed at birth in full term infants although not of adult strength [28]. Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent. However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease. Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48-80]. An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21] but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia.

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full term newborns (III). The highest values were found on the first days after birth. The mean \pm S D on the second day was 1.73 ± 0.38 per cent and on the third day 1.51 ± 0.30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease. The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group. Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn. In this group the bilirubin concentration was 23.4 ± 6.4 mg per 100 ml (range 10-36.2) and the COHb level 1.23 ± 0.28 per cent. Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest. The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility. This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group.

Full term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III). The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0.08 per cent COHb) was statistically significant. This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility. The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level. Thus, Wranne was not able to show any difference between the CO elimination in "ABO incompatible" infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r=0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4-6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

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A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of

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Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

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level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants. A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days. After the first day the association between the COHb and the rate of bilirubin increase was less marked.

Rh haemolytic disease was the only group investigated in which significant anaemia occurred. It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis in this group. The bilirubin production is, however, also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase.

*On the endogenous CO formation in infants of ABO heterospecific pregnancies
(III IV V)*

About one fifth of all pregnancies are ABO heterospecific that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells. In many cases anti A and/or anti B with "immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20-38]. The ABO antigens are usually well developed at birth in full term infants although not of adult strength [28]. Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent. However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease. Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48-80]. An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21], but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia.

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full-term newborns (III). The highest values were found on the first days after birth. The mean \pm S.D. on the second day was 1.73 ± 0.38 per cent and on the third day 1.51 ± 0.30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease. The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group. Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn. In this group the bilirubin concentration was 23.4 ± 6.4 mg per 100 ml (range 10-36.2) and the COHb level 1.23 ± 0.28 per cent. Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest. The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility. This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group.

Full term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III). The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0.08 per cent COHb) was statistically significant. This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility. The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level. Thus, Wranne was not able to show any difference between the CO elimination in "ABO incompatible" infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r=0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4-6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease, and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of

circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al*. The influence of exogenous CO is of particular importance since it may be extremely variable and may

surpass the effect of the endogenous CO formation considerably. Systematic determinations of the CO concentration in room air in the Children's hospital and the Obstetric Department indicated that the average contribution made by exogenous CO to the COHb level was comparatively small, approximately amounting to 15-20 per cent of the normal mean level. Similar determinations should be done in each hospital where COHb is used in the study of haemolytic diseases and should be repeated from time to time. If the CO content in the ambient air is high and variable it can be determined together with the COHb and accounted for.

Smokers often have COHb levels far in excess of those found in haemolytic disease. Patients should not be allowed to smoke during 1-2 days preceding an investigation. With regard to the efficient CO elimination found from the first day after birth the COHb level can be used as an index of haemolysis after 1-2 days in an infant whose mother is a smoker.

Coburn *et al* stressed the effect of the pulmonary CO elimination on the relation between the COHb level and the endogenous CO production and estimated that possible variations in ventilation and diffusing capacity should influence this relationship considerably [12]. The present investigation indicated that in newborn infants without signs of pulmonary disease the influence of these factors was less varying. A close correlation was found between COHb and CO elimination per kg body weight ($r=0.91$). In a steady state the COHb level thus can be assumed to give accurate information about the endogenous CO formation. If the CO production increases the COHb level and the CO elimination will rise rapidly and a new steady state is probably reached within a few hours. In the case of decreasing CO production the time lag in the CO elimination delays the new equilibrium by about 24 hours.

It has been shown that fetal blood has an increased affinity for oxygen when compared

with that of the adult [3]. This phenomenon was long assumed to be caused by the fetal haemoglobin but recent investigations indicate that the high affinity does not depend on the fetal haemoglobin *per se* but is a property of the red cells [3]. The affinity for oxygen influences the equilibrium described by Haldane's equation. In this context the affinity of fetal blood for carbon monoxide is also of importance. Available information on this subject is scanty. Engel *et al* have recently reported that fetal haemoglobin has a lower affinity for CO than adult haemoglobin [17], but did not give the difference or describe their experimental procedure. These properties of the fetal blood can be assumed to reduce the numerical value of the constant in Haldane's equation. Direct determination of the constant in fetal blood is however necessary for the estimation of the effect on the COHb level. In this presentation the possible difference between fetal and adult blood has therefore been disregarded.

The present investigation has shown that the indirect estimation of the endogenous CO formation from the CO saturation of blood is of value in the study of haemolytic diseases and of the pathogenesis of jaundice in newborn infants. A comparison of groups of patients should disclose even moderate differences in the rate of haemoglobin catabolism especially if the groups are examined under the same environmental conditions. In the individual the COHb level reveals an increased haemolysis in the majority of cases. The COHb level also allows a quantification of the rate of haemolysis, but the random error of an estimate of haemolysis from COHb seems to be relatively large.

SUMMARY

Carbon monoxide is a normal metabolite of the haemoproteins and the endogenous formation of CO mainly reflects the haemoglobin catabolism. The endogenous CO production was studied in newborn infants indirectly by determination of the CO saturation of blood

(COHb). Several factors may influence the COHb level in blood and the effect of some of these factors was investigated.

The CO content in the ambient air was determined systematically during a period of one year. The average influence of exogenous CO in the Children's hospital was estimated to be approximately 0.15 per cent COHb or about one fifth of the normal mean level.

Simultaneous determinations of the COHb level and the pulmonary CO elimination showed an efficient CO elimination during the newborn period. In newborn infants without respiratory disease increased COHb values are not caused by CO retention.

A significant correlation was found between the COHb level and the rate of haemolysis calculated from the CO elimination and the total haemoglobin. Theoretical considerations suggested that the COHb/Hb ratio is a better index of haemolysis than COHb. The results of the present investigation supported this hypothesis. This would imply that in the case of anaemia the COHb level underestimates the rate of haemolysis.

In full-term healthy newborns without appreciable jaundice an increased COHb level was found compared with that in adults. Determination of the CO elimination also indicated an increased haemoglobin catabolism in these infants.

In icteric infants without blood group incompatibility an increased COHb level and CO elimination were found, both significantly correlated to the bilirubin concentration. This indicates that an increased bilirubin production contributed to the hyperbilirubinaemia.

In infants with Rh haemolytic disease very high COHb values were often found. The COHb level was correlated to the severity of the disease. Increased COHb values during the first day after birth were usually associated with a rapid rise of the bilirubin concentration.

Determination of the COHb level in infants of ABO heterospecific pregnancies indicated that an increased haemoglobin catabolism was frequent in connection with ABO incompatibility

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ACTA SUPPLEMENT 188 1969
PÆDIATRICA
SCANDINAVICA

**STUDIES IN GLUCOSE GALACTOSE
MALABSORPTION**

**A CLINICAL STUDY OF 6 CASES AND
A GENETIC STUDY**

BY GUNNAR W MEEUWISSE AND KERSTIN MELIN

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PRINTED IN SWEDEN BY
Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1969

GLUCOSE-GALACTOSE MALABSORPTION

A Clinical Study of 6 Cases

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In a previous article (28) a case of monosaccharide malabsorption was described. Two more cases were mentioned by us in a preliminary report (31) in which the name of this condition was altered to the more adequate, glucose-galactose malabsorption (GGM). The present paper reports the clinical data of six patients, all being inhabitants of a rather circumscribed area in Northern Sweden. One more case has been found in another part of Sweden (21). Now it is clear however that the condition is not confined to this country. Simultaneously with our first study a group of French investigators observed two cases of what they termed "Intolerance to actively transported sugars" which is evidently the same disease (25). More recently the disorder has been described in other countries (1, 3, 12, 33-35, 48).

CLINICAL PICTURE

Case histories

The clinical material consisted of 6 cases of GGM. Four children without gastro-intestinal disorders and in good health served as controls

for galactose TT's. The individual case histories of the patients with GGM are reported below. Some clinical data are, however presented in Table 1. Pregnancies and births were uneventful for all cases except Case 5 born 2 weeks after term, and Case 6, born with the aid of a vacuum extractor. Routine laboratory findings obtained soon after admission are listed in Table 2. The results of some simple tests on the absorption and excretion of carbohydrates are summarized in Table 3.

Case 1

A girl, born on October 13, 1954, was admitted at 9 days of age due to diarrhoea from her 3rd and vomiting from her 7th day of life.

History before admission. Breast milk and additional cow milk was given for the first four days of life. Subsequently only high casein formula containing sucrose and lactose was given. The frequent stools kept their watery consistency.

On admission, weighing 500 g less than at birth, her general condition was good. Spontaneous motility was lively and she ate with a good appetite. She had a vigorous cry. Physical examination: *ad.*, except a moderate decrease of turgor.

Serum chloride was high. The low serum sodium content was probably erroneously measured (Table 2). Acidosis was present. There was slight proteinuria and a positive Chabuz test. Later on the proteinuria disappeared but the glucosuria persisted. The urinary sediment was normal.

Course in the hospital. Diarrhoea and vomiting continued on feeding with equal amounts of breast milk and tea containing 5 per cent glucose. After 2 days a soy flour formula with sucrose as the main

Abbreviations: GGM, glucose-galactose malabsorption; GTT, glucose tolerance test; PEG, polyethylene glycol; THL, trihydroxymethyl santonemethane; TT, tolerance test (with oral load of sugar other than glucose).

Table 1 Main clinical data in six cases with glucose-galactose malabsorption

Case no.	Present age	Age at first hospitalization (days)	Diet before admission	Age at onset of diarrhoea (days)	Birth weight (g)	Weight at admission (kg)	Fever (above 38°C)	Vomiting	Diet result in amelioration	Additional disorders
1	9 ys	9	Breast milk and a formula with sucrose	3	3650	3150	+	+	Mullikoy Sobee	Renal concretions
2	† 2 mos	50	Breast milk and a formula with sucrose	"few"	3500	2790	-	+	-	Candida infection of mouth, Nephrocalcinosis, Renal concretions
3	42 ys	9	Breast milk	1	4000	?	?	-	Formula with water, milk, celite, sucrose (Mullikoy)	Renal concretions
4	7 ys	5	Breast milk	4	3370	2690	+	-	Fructose (or Fructose formula)	Candida infection of mouth, Hypoparathyroidism, Pulmonary disease, Myocarditis, Staphylococcus dermatitis
5	† 3 mos	5	Breast milk	4	3600	3100	-	-	Fructose formula	
6	6 ys	4	Breast milk	2	4100	3500	+	-	Fructose formula	

† Deceased

carbohydrate (Mullikoy®) was given. The symptoms ceased and she started to gain in weight but increments soon diminished. Additional glucose solutions exceeding a concentration of 3 per cent result in loose stools.

During this period, while the patient was in reasonable balance, the serum electrolyte, acid-base balance, serum protein, haematocrit and NPN values were normal. The fasting blood sugar varied between 70 and 110 mg/100 ml as measured by a reduction method (16). GTT and galactose TT resulted in flat curves. After the galactose TT increased diarrhoea was observed, and small amounts of urinary glucose were found whereas urinary galactose was absent.

At 3 months, when her weight was 4000 g breast milk feeding was retried. Again frequent stools resembling urine resulted and she became severely dehydrated. A slight fever was observed. Acidosis and dehydration were more pronounced than at admission (cf Table 2): HCO_3^- 5 mEq/l, Na 149 mEq/l, NPN 63 mg/100 ml and protein 6.7 g/100 ml. The paper electrophorogram was normal. The Clinistix test on the watery stools was strongly positive whereas it was negative on urine. She received glucose and electrolytes intravenously: orally she was given small amounts of breast milk, and tea containing 2.5 per cent fructose. The latter monosaccharide was chosen because empirically glucose had been found to be harmful in this case. Several formulae were then tried to no benefit. Finally a soy flour formula (Sobee®), containing corn sugar and sucrose, was given again. From that time (6 months) she gained weight steadily and the stools became semisolid. Other foods were introduced: fish, meat, eggs. Most fruit juices and vegetables were well tolerated, while grape juice, winter carrots and starch gave diarrhoea. At times glucosuria was found with the Clinistix test with no correlation with the clinical state. When the patient was dismissed from the hospital at the age of 8 months, she weighed 6490 g and her psychomotor development was normal.

History after discharge The further course has been characterized by short periods of diarrhoea especially after ingestion of milk and starch-rich foods. An attack of pyelitis occurred at 3 years and she was again given hospital treatment. The intravenous pyelogram revealed stones in the left ureter and a left-sided hydronephrosis. Upon reinspection of an abdominal X-ray made when she was 4 months old, small renal concretions were visible. Four stones were removed by surgery one of the stones contained calcium oxalate and the others calcium phosphate. Urinary excretion of calcium and phosphorus was normal. Endogenous creatine clearance was 1.4 ml/min/1.73 sqm and maximal specific gravity of the urine after pitressin administration was 1025. Renal acidifying capacity (53) was tested at 6 years of age and found to be impaired, the lowest pH after ammonium chloride administration being 5.6.

At several check-ups her mental and physical development was found to be normal (8 years, weight 20.3 kg and height 120 cm). Her diet is restricted in

Table 2. Various laboratory findings soon after admission in five cases with glucose-galactose malabsorption.

Case no.	Serum electrolytes, (mEq/l)				NPN (mg/100 ml)	Serum Protein (g/100 ml)	Hb (g/100 ml)	RBC 10^6	WBC (cells/mm ³)
	Na	K	Cl	HCO ₃					
1	134	5.8	120	12	53	6.2	21.5	6.0	18,400
2	166	4.2	—	—	—	—	13.2	4.1	7,500
4	160	5.3	130	16	50	7.3	19.6	6.0	11,300
5	—	—	—	—	—	7.4	18.3	5.1	17,200
6	173	5.8	120	9.5	78	7.6	20.2	6.8	13,500

Serum creatine was 1.1 mg/100 ml.

milk and starch-containing foods and, for sweetening, fructose is used in place of sucrose.

Case 2

A girl, born on January 26, 1957, an elder sister of Case 1 was admitted at 7 weeks of age because of diarrhoea and vomiting from her 4-5th day.

History before admission. Owing to continuous diarrhoea, whereby she lost 400 g in weight during the first week of life, breast feeding was stopped at about 2 weeks of age and instead different cow's milk formulas containing sucrose and wheat flour or corn starch were tried. Tea with glucose was also given without amelioration of the diarrhoea or the vomiting. She continued to lose weight.

On admission her general condition was severe. She had the appearance of a chronically ill and severely malnourished child. She had no fever. The pulse rate was 135/min. The skin was pale and dry with a decreased turgor. Besides thrush stomatitis she had a sore throat and physical signs of bronchitis. The abdomen was meteoric. The chest X-ray was normal whereas the abdominal X-ray showed dilated, gas filled loops with no signs of obstruction. The ECG was normal. Slight albuminuria and leucocyturia were demonstrated and the urine also contained reducing substance as measured by Abbot's method (2, 41). Serum sodium was increased (Table 2).

Course in the hospital. She was treated with intravenous glucose and electrolytes and, in addition, penicillin and blood transfusions. The diet was altered to breast milk, given in small amounts. The following day her general condition was slightly improved despite continued watery diarrhoea and occasional vomiting. On the third day after admission she suddenly became worse with impaired breathing and consciousness, and died soon after.

Autopsy revealed moderately dilated small-intestine loops, containing watery yellow non-offensive, non-coagulating fluid. The same fluid was present in the proximal colon, and distally some semisolid greenish material was found. There were no signs of necrosis. Cultures revealed non-pathogenic *E. coli* and *Enterococcus*. The liver was considered to be

slightly enlarged and somewhat pale. The bile tract was normal as was the pancreas. Gross anatomy of the kidneys was normal with the exception of several very pale, small areas within the papillary region. At microscopy these areas were found to contain crystalline material within the distal tubules and adjacent interspaces (nephrocalcinosis). The posterior basal segments of the lungs were ectatic; microscopically the distal airways contained an exudate of leukocytes. The heart was normal. The brain showed no significant abnormalities. The immediate cause of death could not be established.

Case 3

A woman, born on October 2, 1926 was discovered to be case of GGM when the heredity of Case 1 and 2 was penetrated: she was distantly related to them.

History before (actual) admission. Being breastfed, watery diarrhoea began immediately. At 9 days of age she was admitted to cottage hospital, where a buttermilk formula and whole milk formula were tried without any improvement. Since the baby's condition became worse, she was taken home and her mother made a formula of water, small amounts of cow's milk, oats and sucrose. Given that the baby began to gain in weight for the first time and at 4 months she weighed 3800 g. From 6 months of age she also ate fish, meat and eggs mixed with cream and water. She slowly increased in weight but during infancy she always had loose stools and a large abdomen. At one year of age she was seen by the local practitioner. His diagnosis was celiac disease and he forbade milk and cereals. Later during childhood she maintained tendency towards loose stools, and was often abnormally thirsty. Menarche occurred at 20 years.

In adulthood she still has digestive problems. More than half glass of milk results in abdominal cramp and loose stools. Bread, peas and more than one potato give the same symptoms. Some fruit such as bananas, apples and oranges also cause abdominal cramps. On diet chiefly consisting of fish, meat, cream, butter and porridge and not more than one slice of bread per meal she is symptom-free.

Since the age of 10 she experienced low back pain. There is no evidence of osteoporosis on X-ray examinations. At the age of 12 the patient had epidemic hepatitis without sequelae. At 32 years she was operated for toxic struma and then renal glucosuria was noted for the first time. GTT's were flat.

On admission she was 36 years old and in a good mental and physical state (body weight 66 kg; height 177 cm). The diagnosis of GOM was confirmed by an intestinal intubation study which showed that glucose was absorbed more slowly than fructose (29). Results of studies on mucosal biopsy specimens have been published elsewhere (37).

History after discharge At 38 years of age the patient had colics during passage of small renal concretions. On a second occasion the stone was collected and analyzed; it contained calcium, ammonium, oxalate and phosphate. All concretions passed spontaneously. There were no other abnormalities at X-ray examination or on an intravenous pyelogram.

Case 4

A girl, born on September 7 1961 was admitted at 18 days of age owing to diarrhoea from her 4th day. The patient has previously been described in detail (28).

History before admission She was breastfed for one week. From her 5th day she was treated at the pediatric department of another hospital. Due to continuous diarrhoea with watery stools resembling urine, several formulas containing different sugar contents were tried instead. Parenteral fluid was also given.

On admission her general condition was good and there were no signs of dehydration. Spontaneous motility was lively and she had a good appetite. Serum electrolytes were increased and there was a moderate acidosis (Table 2). Clinistix reaction on urine was positive. Glucose was demonstrated in the feces.

Course in the hospital She improved on a soy flour formula with a low carbohydrate content (Milibroy®). During the first half year she suffered frequent infections of the respiratory tract. The Clinistix reaction on the urine was sometimes weakly positive, sometimes negative. Different oral sugar loading tests were performed. The results of these, as well as of an intubation study leading to the diagnosis of glucose-galactose malabsorption, have been published elsewhere (28).

When, at about 6 months of age, she was given a fructose formula (30) the stools immediately became normal. Solid foods were introduced at 7 months and the daily volume of the fructose formula could successively be reduced. She weighed 7000 g when discharged from the hospital at 9 months of age.

History after discharge This was rather uneventful. To avoid loose stools she had, however to be maintained on a diet with certain limitations regarding milk and starch-containing foods. Oats seemed to be better tolerated than other cereals. From the age of 1 year she ate fructose formula only once or twice a

day. At 2 years she could tolerate 1 glass of milk, 2 sandwiches and 2 potatoes a day spaced over several meals, without any trouble. When 3 1/2 years old her height was 107 cm and weight 17.9 kg. Physical and mental development was perfectly normal. She tolerated 2 glasses of milk a day 3-4 sandwiches and 3 potatoes. All fruits except grapes could be eaten without adverse consequences.

Case 5

A boy born on March 30, 1964 a younger brother of Case 4, was admitted at 4 days of age because of diarrhoea noted from the 4th day.

History before admission. He was born 7 weeks after term and he had been breast fed. Due to severe diarrhoea, the stools resembling urine, he was transferred from the maternity hospital to the department of pediatrics.

On admission he weighed 500 g below his birth weight but his general condition was satisfactory. Spontaneous motility was lively and he had a good appetite. He had a moderate decrease of uric acid. The presence of glucose in the stools and in the urine was demonstrated with the Clinistix test. Some other laboratory data are shown in Table 2.

Course in the hospital Breast feeding was stopped and the infant instead received a fructose formula (30). The stools immediately became normal and the patient began to gain in weight.

The GTT and galactose TT resulted in flat blood glucose curves, the fructose TT indicated a normal fructose absorption (Table 3 and 5).

History after discharge For the next few months the patient was well. At 3 months of age he acquired a stomatitis, which was unsuccessfully treated with Chloromycetin, and he was therefore readmitted to the hospital.

On (second) admission he had a severe *Candida* infection in his mouth. His general condition worsened successively and the *Candida* infection spread to the skin. Soon he showed signs of respiratory insufficiency and the chest X-ray revealed pulmonary infiltrations.

ESR was 21 and the WBC varied between 22,500 and 8000. The differential count was normal (lymphocytes 53 and 66 per cent on two occasions). The total serum protein was low (4.1 g/100 ml). The paper electrophoretogram, which had been normal at 2 weeks of age, was pathological with a borderline low albumin value (3.1 g/100 ml) and a low gamma globulin value (0.1 g/100 ml). The α_2 -globulin was relatively elevated (0.4 g/100 ml), whereas the α_1 and the β -globulins were normal. The patient was found to have anti A and anti B isoenzymes in his

After a modification with regard to salts this formula contains Calcium caseinate 2.3%, corn oil 3.5%, fructose 4-8%, and furthermore, per liter for mola 1 Tsp. of a salt mixture (KCl, NaCl, CaHPO₄, 2H₂O mixture 2 1 1 w/w), 1 Tabl. Milnovit® (a multivitamin and trace mineral preparation) and 1/2-1 Tsp. Nestargel® for adjustment of consistency

serum. On the immunoelectrophoresis there was weak γ -G band, γ -A and γ -M could not be distinguished. The patient died rather suddenly after two weeks in the hospital; he was thought to have asphyxiated during coughing.

Autopsy. No signs of widespread *Candida* infection of the gut or respiratory tract were found. The basal parts of the lungs were atelectatic; microscopically there are atelectatic parts in other lung segments too. An unspecific inflammatory picture with giant cells was seen in the bronchi with surrounding peribronchitis, no epithelioid cells were found, and no crypts were visible with special staining. The histological picture resembled *Pneumocystis Carinii* infection, but this organism was absent in the specimens. The thymus was macroscopically normal and weighed 5 g. Microscopically there was a rather marked atrophy of the lymphoid component of this organ. Lymph nodes from different parts of the body showed lymphoid atrophy with very small and indistinct secondary follicles and few reaction centres. The spleen showed atrophic Malpighian corpuscles without reaction centres. The histological preparations of the bone marrow were difficult to interpret with respect to the presence of small lymphocytes or plasma cells. The small intestine was strongly atrophic. There were no lymph follicles.

Case 6

A boy born on May 24, 1962, was admitted at 4 days of age because of diarrhoea from his 2nd day and fever from his 3rd day of life.

History before admission. A vacuum extractor was used at the otherwise normal delivery. He was breast-fed for one week. Due to watery diarrhoea he lost 600 g of his weight in 4 days. A temperature of 38.4°C was recorded at the maternity department.

On admission, his general condition was fairly good, although a moderate decrease of skin turgor was observed. Spontaneous motility was lively and he had good appetite.

The Clinitest test on the feces was strongly positive. Nearly 6 g of sugar, 2.7 g of which was glucose, was found per 100 g wet feces. The Clinitest test on the urine was sometimes positive and sometimes negative. Albuminuria was observed during the first 2 days after admission. At the same time the urinary sediment contained considerable quantity of red and white blood cells and abundant crystals, but new sediment few days later was found to be normal. It was doubtful if the urinary tract was infected; sulfonamides were, however, given for few days.

Course in the hospital. He continued to have profuse watery diarrhoea, and during the 4 days after admission he lost an additional 230 g in weight. By then he looked dehydrated and his motility decreased. The peripheral circulation seemed poor. Hyperreflexia and metabolic acidosis were found (Table 2). The ECG was normal. During rehydration with intravenously administered fluid he

had convulsions for 25 minutes. H increased his weight by 460 g within two days.

Replacement of mother's milk by a fructose for formula (30) was followed by diminished diarrhoea and a fall of the fecal sugar content to less than 0.03 per cent of wet weight. The diet was abandoned, however, because of vomiting and weight loss.

When the baby was 2 weeks old, tachycardia and ectricular extrasystoles were observed and general adynamia occurred. Serum potassium was normal and there were no signs of hypokalaemia on the ECG. Nevertheless, potassium chloride was given orally. The next day pulmonary congestion and a considerable enlargement of the heart was seen on X-ray. During the next few days the tachycardia increased and the liver became enlarged. Shifting ECG findings occurred with increased PR-interval, transient extrasystoles and negative T-waves over the left ventricle. The pulse rate and heart size gradually became normal during the following weeks. The clinical course of this complication was consistent with the diagnosis of infantile myocarditis. Virus isolation from the feces was negative and the serum did not contain neutralizing antibodies against Cox-Sackie B virus. Feces cultures showed pathogenic strain of *E. coli*, and the patient was given broad spectrum antibiotics. In a few days he developed a widespread staphylococcal dermatitis in the face and the axillary regions. The feces now contained dominating flora of *Staphylococcus aureus*.

The diet had been changed to soy flour formula with a low carbohydrate content (Mullhøj 8) with extra amounts of water. Weight gain was slow and he had 2-3 semisolid stools a day. From 1 month of age limited amounts of the fructose formula were added without ill effects.

At the age of about two months a definite diagnosis of GGM was secured by oral sugar loading tests including GTT and galactose TT which resulted in flat blood sugar curves and increased fecal sugar. From that age the patient was consequently fed the fructose formula (30) after which the diarrhoea subsided. He was nearly 10 weeks old when he finally attained his birth weight again. Subsequently his growth was rapid and he gradually reached a normal weight in relation to his length. He was discharged at 6 months of age when his body weight was 6500 g.

History after discharge. The daily amounts of the fructose formula could be reduced as the amount of solid food was successively increased. At the age of 1 year he received about 200 g of the fructose formula twice a day. Otherwise he ate eggs, fish, meat, vegetables and fruit. He tolerated up to 300 ml of cream a day. He refused oral porridge which earlier he had tolerated in limited amounts. He also disliked potatoes. One slice of white bread resulted in diarrhoea.

Successive studies showed that the physical and mental development of this boy has been normal. At 5 1/2 years of age he was 112 cm tall and weighed 17 kg. His belly has tendency to swell when he eats

Since the age of 10 she experienced low back pain. There is no evidence of osteoporosis on X-ray examinations. At the age of 12 the patient had epidemic hepatitis without sequelae. At 32 years she was operated for toxic struma and then renal glucosuria was noted for the first time. GTTs were flat.

On admission she was 36 years old and in a good mental and physical state (body weight 66 kg; height 177 cm). The diagnosis of GGM was confirmed by an intestinal intubation study which showed that glucose was absorbed more slowly than fructose (29). Results of studies on mucosal biopsy specimens have been published elsewhere (37).

History after discharge At 38 years of age the patient had colics during passage of small renal concretions. On a second occasion the stone was collected and analyzed, it contained calcium, ammonium, oxalate and phosphate. All concretions passed spontaneously. There were no other abnormalities at X-ray examination or on an intravenous pyelogram.

Case 4

A girl born on September 7 1961 was admitted at 18 days of age owing to diarrhoea from her 4th day. The patient has previously been described in detail (28).

History before admission She was breastfed for one week. From her 5th day she was treated at the pediatric department of another hospital. Due to continuous diarrhoea with watery stools resembling urine, several formulae, containing different sugar contents were tried instead. Parenteral fluid was also given.

On admission her general condition was good and there were no signs of dehydration. Spontaneous motility was lively and she had a good appetite. Serum electrolytes were increased and there was a moderate acidosis (Table 2). Clinistix reaction on urine was positive. Glucose was demonstrated in the feces.

Course in the hospital She improved on a soy flour formula with a low carbohydrate content (Mullhoy®). During the first half year she suffered frequent infections of the respiratory tract. The Clinistix reaction on the urine was sometimes weakly positive, some times negative. Different oral sugar loading tests were performed. The results of these, as well as of an intubation study leading to the diagnosis of glucose-galactose malabsorption, have been published elsewhere (28).

When, at about 6 months of age, she was given a fructose formula (30) the stools immediately became normal. Solid foods were introduced at 7 months and the daily volume of the fructose formula could successively be reduced. She weighed 7000 g when discharged from the hospital at 9 months of age.

History after discharge This was rather uneventful. To avoid loose stools she had, however to be maintained on a diet with certain limitations regarding milk and starch-containing foods. Oats seemed to be better tolerated than other cereals. From the age of 1 year she ate fructose formula only once or twice a

day. At 2 years she could tolerate 1 glass of milk, 2 sandwiches and 2 potatoes a day spaced over several meals, without any trouble. When 5 years old her height was 107 cm and weight 17.9 kg. Physical and mental development was perfectly normal. She tolerated 2 glasses of milk a day 3-4 sandwiches and 3 potatoes. All fruits except grapes could be eaten without adverse consequences.

Case 5

A boy born on March 30, 1964 a younger brother of Case 4 was admitted at 4 days of age because of diarrhoea noted from the 4th day.

History before admission. He was born 2 weeks after term and he had been breast fed. Due to severe diarrhoea, the stools resembling urine, he was transferred from the maternity hospital to the department of pediatrics.

On admission he weighed 500 g below his birth weight but his general condition was satisfactory. Spontaneous motility was lively and he had a good appetite. He had a moderate decrease of turpore. The presence of glucose in the stools and in the urine was demonstrated with the Clinistix test. Some other laboratory data are shown in Table 2.

Course in the hospital. Breast feeding was stopped and the infant instead received a fructose formula (30). The stools immediately became normal and the patient began to gain in weight.

The GTT and galactose TT resulted in flat blood glucose curves. The fructose TT indicated a normal fructose absorption (Table 3 and 5).

History after discharge. For the next few months the patient was well. At 3 months of age he acquired a stomatitis, which was unsuccessfully treated with Chloromycetin, and he was therefore readmitted to the hospital.

On (second) admission he had a severe *Candida* infection in his mouth. His general condition worsened successively and the *Candida* infection spread to the skin. Soon he showed signs of respiratory insufficiency and the chest X-ray revealed pulmonary infiltrations.

ESR was 21 and the WBC varied between 22,500 and 8000. The differential count was normal (lymphocytes 53 and 66 per cent on two occasions). The total serum protein was low (4.1 g/100 ml). The paper electrophorogram, which had been normal at 2 weeks of age, was pathological with a borderline low albumin value (3.1 g/100 ml) and a low gamma globulin value (0.1 g/100 ml). The α 2 globulin was relatively elevated (0.4 g/100 ml), whereas the α 1 and the β globulins were normal. The patient was found to have anti A and anti B isogglutinins in his

After a modification with regard to salts this formula contains Calcium caseinate 2.3%, corn oil 3.5%, fructose 4-8%, and furthermore, per liter for mola I Tsp. of a salt mixture (KCl, NaCl, CaHPO₄, 2H₂O mixture 2 1 1 w/w), 1 Tabl. Minovi® (a multivitamin and trace mineral preparation) and 1/4 Tsp. Nestargel® for adjustment of consistency.

serum. On the immunoelectrophoresis there was weak γ -G band, γ -A and γ -M could not be distinguished. The patient died rather suddenly after two weeks in the hospital; he was thought to have asper and during cooling.

Autopsy No signs of widespread *Candida* infection of the gut or respiratory tract were found. The basal parts of the lungs were atelectatic; microscopically there are atelectatic parts in other lung segments too. An nonspecific inflammatory picture with giant cells was seen in the bronchi with surrounding parenchyma, no epithelioid cells were found, and no myocitis were visible with special staining. The histological picture resembled *Paramecystis* Carial infection, but this organism was absent in the specimens. The thymus was macroscopically normal and weighed 5 g. Microscopically there was rather marked atrophy of the lymphoid component of this organ. Lymph nodes from different parts of the body showed lymphoid atrophy with very small and indistinct secondary follicles and few reactive centers. The spleen showed atrophic Malpighian corporcles without reaction centres. The histological preparations of the bone marrow were difficult to interpret with respect to the presence of small lymphocytes or plasma cells. The small intestine was strongly atrophic. There were no lymph follicles.

Case 6

A boy born on May 24, 1962, was admitted at 4 days of age because of diarrhoea from his 2nd day and fever from his 3rd day of life.

History before admission. A vacuum extractor was used at the otherwise normal delivery. He was breast fed for one week. Due to watery diarrhoea he lost 600 g of his weight in 4 days. A temperature of 38.4°C was recorded at the maternity department.

On admission, his general condition was fairly good, although a moderate decrease of skin turgor was observed. Spontaneous motility was lively and he had good appetite.

The *Claibitz* test on the feces was strongly positive. Nearly 6 g of sugar, 2.7 g of which was glucose, was found per 100 g wet feces. The *Claibitz* test on the urine was sometimes positive and sometimes negative. *Allothrombosis* was observed during the first 2 days after admission. At the same time the urinary sediments contained considerable quantity of red and white blood cells and abundant crystals, but new sediment few days later was found to be normal. It was doubtful if the urinary tract was infected, anticonvulsants were, however, given for few days.

Course in the hospital. He continued to have profuse watery diarrhoea, and during the 4 days after admission he lost an additional 230 g in weight. By then he looked dehydrated and his motility decreased. The peripheral circulation seemed poor. Hypernatremia and metabolic acidosis were found (Table 2). The ECG was normal. During rehydration with intravenously administered fluid he

had convulsions for 25 minutes. He increased his weight by 460 g within two days.

Replacement of mother's milk by a fructose for milk (30) was followed by diminished diarrhoea and a fall of the fecal sugar content to less than 0.03 per cent of wet weight. The diet was abandoned, however because of vomiting and weight loss.

When the baby was 2 weeks old, tachycardia and ventricular extrasystoles were observed and general adynamia occurred. Serum potassium was normal and there were no signs of hypokalemia on the ECG. Nevertheless, potassium chloride was given orally. The next day pulmonary congestion and a considerable enlargement of the heart was seen on X-ray. During the next few days the tachycardia increased and the liver became enlarged. Shifting ECG findings occurred with increased PR-interval, transient extrasystoles and negative T-waves over the left cuticle. The pulse rate and heart size gradually became normal during the following weeks. The clinical course of this complication was consistent with the diagnosis of infantile myocarditis. Virus isolation from the feces was negative and the serum did not contain neutralising antibodies against Coxsackie B virus. Feces cultures showed pathogenic strains of *E. coli*, and the patient was given broad spectrum antibiotics. In a few days he developed widespread staphylococcal dermatitis in the face and the axillary regions. The feces now contained dominating flora of *Staphylococcus aureus*.

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History after discharge. The daily amounts of the fructose formula could be reduced as the amount of solid food was successively increased. At the age of 1 year he received about 200 g of the fructose formula twice a day. Otherwise he ate eggs, fish, meat, vegetables and fruit. He tolerated 10 to 300 ml of cream a day. He refused oat meal porridge which earlier he had tolerated in limited amounts. He also disliked potatoes. One slice of white bread resulted in diarrhoea.

Successive studies showed that the physical and mental development of this boy has been normal. At 5 1/2 years of age he was 112 cm tall and weighed 17 kg. His belly has a tendency to swell when he eats

unsuitable food. He then experiences abdominal pains but loose stools do not always follow. The symptoms are provoked by foodstuffs rich in ordinary sugar or still more by starch. Milk is tolerated fairly well. He still dislikes potatoes, but eats large quantities of vegetables and fish every day. From 3 1/2 years of age no fructose has been added to his diet.

Relevant symptoms and signs of Glucose Galactose malabsorption as evaluated from the case histories

The patients have had several features in common (Table 1-3). The diarrhoea started within a few days after birth. The time of onset varied a little, probably depending on how much the babies suckled. They gradually became dehydrated and often a moderate fever was noted. The general condition was always remarkably good in the beginning, and the cases observed by us from an early age had a striking appetite, probably depending on thirst, as long as they were not extremely dehydrated. The stools were watery and resembled urine, giving rise in some cases, to a strong suspicion of a congenital communication between the rectum and the urinary tract.

The stools always contained several per cent of carbohydrate. The Clinistix test (specific for glucose) on the watery stools was strongly positive. The blood glucose level was usually low during the first months of life (Table 3) and after breast milk or ordinary formula feeding it did not rise above the fasting level.

The Clinistix test on urine was sometimes positive and sometimes negative independent of the clinical state.

Before the diagnosis was recognized, the patients usually have been dietetically treated as having severe gastroenteritis. During periods of intravenous nutrition oral amounts of glucose seemed to be tolerated as long as the concentration was below 2-3 per cent. Similarly small amounts of breast milk were fairly well tolerated, unless given as the main nutritional source, when the patient soon deteriorated. The prompt cessation of the watery diarrhoea when fructose was given as a substitute for all

other dietary carbohydrates was always quite remarkable.

Mental and physical development after cessation of continuous diarrhoea has been normal in all surviving patients.

Besides the sugar diarrhoea and the slight glucosuria, additional illnesses occurred in 5 patients (Table 1). Renal concretions occurred in Cases 1 and 3. In Case 2 nephrocalcinosis was found at autopsy. Fungus infection with *Candida albicans* was found in two cases. Both of these died. This rather common stomatitis in early infancy did not seem to have contributed to the death of Case 2. In Case 5 the fungus infection spread to the skin, but at autopsy there were no signs of invasion of internal organs.

BIOCHEMISTRY OF INTESTINAL FUNCTION

Methods

Reagents

Analytical grade reagents were used for the chemical analyses. Sugars were obtained from May & Baker Ltd., Dagenham, England, from Pfaltz & Glaser Laboratories Inc., Wheeling, Ill. USA and from Mallinkrodt Chem. Works, New York, N.Y. USA. Buffers were prepared as proposed by Gomori (13) using reagents from Merck A. G. Darmstadt, Germany. TRIS, however, was purchased from Sigma Chem. Co. St. Louis, Mo. USA. Peroxidase (horse-radish) also came from Sigma. Glucose oxidase (crude) was obtained from Worthington Biochem. Corp., Freehold, N. J. USA. Galactose oxidase was from the same source initially but was later replaced by the preparation of Miles Chem. Co., Elkhart, Ind. USA. O-dianilidine (3,3'-dimethoxy benzidine) was obtained from Eastman Org. Chemicals as was p-bromo aniline for the xylose determination. The detergent Cascade was from May & Baker. β -iodole acetic acid for fructose determination was obtained from Merck and so was anthrone. Polyethylene glycol (M.W. 4000) was manufactured by Bergman's fabriker Gnesta, Sweden. The lactase, invertase and maltase preparations were generous gifts from Mycopharm, Delft, Netherlands.

General procedures

Oral sugar tolerance tests: 10% sugar solutions were given in a dose of 2 g sugar/kg body

weight. The adult patient received doses of 50 g. The accuracy in faeces collection during the 48 hours after some of these tests could be estimated by adding 1-5 g of an unabsorbed marker polyethylene glycol (PEG), to the test dose. For the xylose absorption test doses of 15 g D-xylose/sq.m. body surface area were used.

Intubation studies for the measurement of intestinal absorption of sugars were performed with rubber or polyvinyl tubes of an inner diameter of 2 mm, which were passed under fluoroscopic control through the nose into the jejunum. Homogenized test meals of 200-300 ml containing 3% casein, 4% corn oil, salts as present in the fructose formula (*vide supra*), 1% PEG and 4% of various sugar mixtures were given orally. The intestinal contents were siphoned into ice-chilled test tubes and fractions were collected for 2 hours. The test tubes were frozen at -20 C and kept in a deep freezer until analysis was performed.

The percentage digestion and absorption was calculated as per cent of the initial amount of sugar. It was assumed that all the sugar which had been absorbed had also been hydrolysed to monosaccharides. The percentage of disaccharide digested was calculated from the initial amount minus the amount recovered as disaccharide. The percentage of sugar absorbed was calculated from the initial amount minus the amount of this sugar recovered (disaccharide plus monosaccharide). The following equation was used to compensate for volume changes:

$100 \{1 - (P \times S_s) / (P_s \times S_t)\} = \% \text{ digestion or absorption, respectively}$

P and P_s are the concentrations of PEG in the test meal and sample, respectively and S_t and S_s the corresponding concentrations of sugar. PEG concentration was determined according to Hyden (20).

Deproteinization of biological samples. Blood, intestinal content, test meals and suspensions of faeces were precipitated with 2 ml 0.3 N Ba(OH)₂ and 2 ml equimolar ZnSO₄ per 1 ml sample after addition of a suitable amount

of water and were centrifuged or filtered (50). Previous to this method the faeces suspensions had been diluted at least ten-fold with water to obtain clear colourless filtrates after deproteinization.

Sugar determinations

Unspecific methods. 1 Reducing sugar was determined using the Somogyi-Nelson method (51) with relevant sugars as standards. All sugars except sucrose are reducing.

2 Total sugar was measured using an anthrone method (46). All sugars as well as polysaccharides react.

3 Qualitative identification of sugars was done by paper chromatography. Descending chromatograms of some faeces samples were thus made on Whatman 1 paper. The solvent used was a mixture of ethyl acetate, glacial acetic acid and water (9:2:2, v/v). The dried chromatograms were developed with aniline phthalate (45).

Specific methods. 1 Glucose was assayed using a glucose oxidase reagent (10). In the presence of TRIS only free glucose is measured.

2 Galactose was measured similarly to glucose using galactose oxidase. Free galactose, and also lactose to a small extent, act as substrates. If present, corrections were made for lactose content. It must be mentioned that the photometer readings are not quite proportional to the sugar concentration. Hence, standard curves with several concentrations of sugar were made for each set of determinations. The reagent was prepared as follows: 10 mg dry galactose oxidase (Miles), 0.5 mg peroxidase, 0.5 ml o-dianisidine as a saturated solution in alcohol and a detergent, 1 ml Cascade (10% in alcohol), were added to 100 ml potassium phosphate buffer (0.1 M pH 7).

3 Fructose was assayed using Heyrovsky's method (18) measuring keto-sugars and their derivatives (sucrose, inulin). Glucose reacts slightly to about 1.3% of the colour produced by fructose. When appreciable amounts of glucose were present, the appropriate corrections

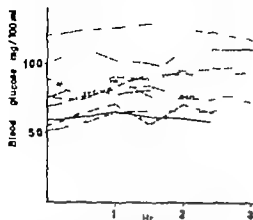


Fig 1 Oral glucose tolerance tests in 5 patients with glucose galactose malabsorption.

Symbols: — Case 1 Case 3 --- Case 4 --- Case 5 - - - Case 6. Note: The maximum increase of blood glucose observed within the first hour in any patient is 21 mg/100 ml.

were made. In one experiment fructose had to be determined in the presence of sucrose, which was determined separately (*vide infra*) and subtracted from the total fructose value to obtain the concentration of free fructose.

4 Xylose was determined according to O'Brien and Ibbott (42).

5 Disaccharides (lactose sucrose and maltose) were assayed enzymatically by measuring the increase in glucose content in a deproteinized and suitably diluted sample on incubation with a disaccharidase preparation.

a. Lactose. A lactase solution was prepared by dissolving 50 mg of dry lactase in 100 ml potassium phosphate buffer (0.1 M pH 6.8). This solution was filtered after 20 minutes intermittent stirring at room temperature. In a test tube 1 ml deproteinized sample (containing less than 100 µg free glucose and lactose-bound glucose) was incubated at 37°C for 20 minutes with 1 ml lactase solution. The increase in glucose content was measured using TRIS glucose oxidase (10). This increase multiplied by a factor of 2 corresponds to the lactose monohydrate content of the sample. Standard solutions of lactose and glucose were treated similarly. In each series of determinations samples with added lactase were included to check that complete hydrolysis by lactase occurred.

6 Sucrose. The disaccharidase solution was made by dissolving 10 mg of dry invertase in 100 ml sodium acetate buffer (0.1 M pH 4.5). As with the lactase determination, samples were incubated with the disaccharidase solution, and the sucrose content was calculated from the increase in the glucose content.

c Maltose. A one-step method was used to determine the maltose monohydrate plus glucose content of the intestinal contents. The reagent was prepared by dissolving 200 mg dry maltase in 50 ml potassium phosphate buffer (0.1 M pH 5.8). The filtered solution was added to 50 ml glucose oxidase reagent prepared using the same buffer. This latter reagent contained 200 mg crude glucose oxidase, 0.5 mg peroxidase, 0.5 ml saturated o-dianisidine in alcohol and 1 ml 10% Cascade (in alcohol). In a test tube 1 ml deproteinized sample (containing less than 50 µg glucose and maltose together) and 2 ml of the maltase glucose oxidase reagent were incubated at 37°C for 60 minutes. Extinctions were read with the same photometer as used for glucose determination at wave length 420 mµ. Standard solutions of maltose and samples with added maltose were treated similarly for each set of determinations. The maltose content was calculated from the glucose estimated, by subtraction of the initially present glucose as assayed using the TRIS glucose oxidase reagent.

Determination of daily fat excretion

Stools were collected for 4-6 days and stored frozen. After homogenization duplicate determinations were carried out by the method of van de Kamer (22).

Results

Response of blood sugar to oral sugar tolerance tests (TT) The results of all GTT's are plotted in Fig. 1. Most of the cases were tested more than once. The curves are flat, but increases in blood sugar up to 21 mg/100 ml within 60 minutes may occur (Table 3).

Galactose TT's were performed in Cases 1, 5 and 6. As seen in Table 4 the rise of galactose was insignificant in comparison with the controls. The rise of glucose was also very small or absent but this was true of the controls too. *Lactose TT's* were performed in Cases 1, 4 and 6; the maximal rise of blood glucose was 16 mg/100 ml (Table 3). In Case 4 a *sucrose TT* was made also (28); the blood glucose rose 42 mg/100 ml during the first hour.

The *fructose TT* performed on the patients soon after admission and before amelioration of the symptoms used to result in significant increase in the blood glucose (Fig. 2). In Case 6 a flatter curve was obtained later on (the

Table 3. *Résumé of routine sugar analyses in six cases with glucose-galactose malabsorption*

Case no.	Blood glucose (fasting value) (mg/100 ml)	Glucose TT max. increase within 60 min (mg/100 ml)	Lactose TT max. increase within 60 min (mg/100 ml)	Sugar in feces (Clinitex)	Sugar in urine
1	70-110*	4	8	+++	±
2	Not done	Not done	Not done	Not done	±
3 ^a	78-110	21	Not done	Not done	±
4	38-75	16	16	++	+++
5	31-80	14	Not done	++	+++
6	57-76	13	1	+++	±

Hagedorn & Jensen method (16). At 3 1/2 years fasting blood sugar was 59-85 with a glucose oxidase method. The other glucose values in this table are obtained with glucose oxidase reagent.

^a Only estimated ab reduction method (2, 4). Other patients measured with Clinitex.[®] Adult patient.

curve with the lowest value at one hour) this patient had for some time been fed a formula with a relatively high fructose content. The significance of different responses in blood glucose after oral fructose loads will be discussed in another paper (38).

Xylose absorption tests have been performed in Cases 5 and 6 (Table 5). The results showed subnormal and borderline values, respectively for xylose in blood (36). The xylose excretion in urine was subnormal too (43).

Fecal sugar measurements after oral sugar loads. Table 6 summarizes the results of fecal sugar measurements following sugar loading tests in Cases 1, 4, 5 and 6. The results of some measurements in Case 6 are also given graphically (Fig. 3). As a check on the chemical determinations some of the stool portions

from Case 6, as indicated by numbers on the columns, were chromatographed (Fig. 4 B). Fig. 4 A is a chromatogram of stool filtrate from the same patient while he was fed breast milk, when the chromatogram was performed the total fecal sugar content amounted to 5 g/100 ml wet feces.

Glucose, galactose and lactose (but not fructose) loads of 2 g/kg body weight, given during the first 6 months of life, consistently resulted in increased diarrhoea with a marked rise in the fecal sugar excretion (Cases 4-6). It should also be noted that the excretion of galactose was always much higher than that of glucose.

In Case 1 (3 1/2 years of age) the GTT was not followed by increased sugar in the stools. The day previous to the performance of the

Table 4. *Oral galactose tolerance tests in 3 patients with glucose-galactose malabsorption and 4 controls*

Galactose values within brackets were measured with the galactose oxidase reagent, the other values with Somogyi-Nelson method with subtraction of blood glucose.

Subject	Sex	Age	Glucose conc. mg/100 ml		Galactose conc. mg/100 ml	
			30 min	60 min	30 min	60 min
Case 1	♀	3 yrs	1	-7	0	0
Case 5	♂	1 1/2 mo	5	4	III	3
Case 6	♂	2 mos	5	-2		
Case 6	♂	5 mos	-3	6	(<10)	(<10)
Control 1		7 mos	2	2	49 (51)	105 (83)
Control 2	♀	1 yr	9	8	45 (43)	110 (140)
Control 3	♂	6 yrs	24	16	66 (56)	78 (73)
Control 4	♀	9 yrs	10	0	15 (29)	83 (91)

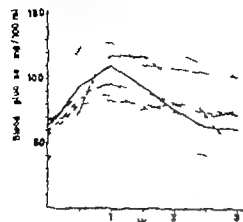


Fig 2 Oral fructose tolerance tests in 5 patients with glucose-galactose malabsorption.

Symbols: — Case 1 Case 3 - - - Case 4 - · - Case 5 · · · Case 2. Note: The increase of blood glucose within the first hour varies considerably (between 7 and 11 mg/100 ml) but usually it exceeds 20 mg/100 ml.

GTT a higher glucose value in the feces was observed, 1.14 % of feces wet weight as compared with 0.07 % at the test, a fact probably due to the diet including a lunch with as a dessert frozen raspberries and sugar. In Case 3 (examined in adulthood) it was considered useless to look for fecal sugars after the oral tolerance tests, since diarrhoea did not result.

Intubation studies These studies were performed in Cases 1, 3 and 4 after intubation of the upper jejunum. Comparison of the glucose and fructose absorption after administration of a test meal containing both of these sugars in equal concentrations was found to be of great value for the diagnosis of GGM. Glucose was always absorbed more slowly than fructose (28, 29). In Cases 1 and 4 intubation studies were also performed with test meals containing

Table 5 Xylose absorption tests in two infants with glucose-galactose malabsorption

Test dose 15 g/sq.m. body surface

Case nr	Age (months)	Blood xylose mg/100 ml		Urinary xylose % of dose excreted in 8 hours
		30 min	60 min	
5	1	9	15	5
6	13	15	25	9

Table 6. Per cent excretion of sugar in feces within 48 hours after oral administration of different sugars (2 g/kg body wt) together with PEG

Subject	Age	Sugar tested	Recovery (% of test dose)	
			Sugar	PEG
Case 5	1/6 mo	Glucose	39	—
		Galactose	83	76
		Fructose	14	58
Case 6	2 mos	Glucose	22	74
		Fructose	0.7	94
		Galactose	53	83
Case 6	5 mos	Glucose	39	84
		Galactose	60	96
		Fructose	0.3	70
		Lactose	10 ^a	48
Case 4	4 mos	Lactose	13.5 ^b	—
	6 mos	Fructose	1.9	—
Case 1	3 / ys	Glucose	0.7	66
		Lactose	< 8.5	96
		Fructose	0.4	116

^a Sum of lactose, glucose and galactose measured with specific enzymatic methods. (1.5 % of the test dose was recovered as the unsplit disaccharide; the rest of the fecal sugar was $\frac{1}{2}$ glucose and $\frac{1}{2}$ galactose.)

^b Sum of lactose, glucose and galactose. Lactose and galactose were measured as excess of sugar found by a reduction method after determination of glucose and fructose with specific methods.

As ^b, but anthrone method for total sugar

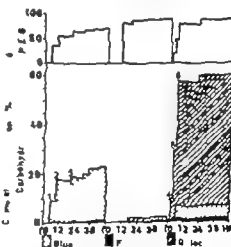


Fig 3 Cumulative excretion in feces of PEG and sugars during 48 hours after oral sugar tolerance tests with glucose, fructose and galactose, respectively in a dose of 2 g per kg body weight, Case 6, aged 2 months. The number on the columns refer to stool portions which were also chromatographed (See Fig. 4B). Note: The fecal excretion of galactose was about 2 / times that of glucose. After the fructose loading only insignificant amounts of sugar (glucose) could be demonstrated.

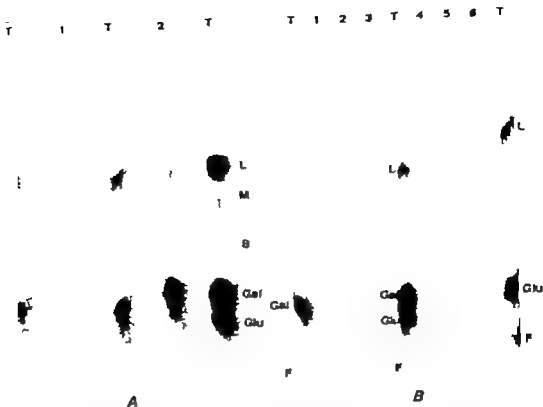


Fig. 4 A, B. Descending paper chromatograms of extracts of feces (starting points at the top of the figure). Symbols: T sugar test solutions; L, lactose; M, maltose; S, sucrose; Gal, galactose; Glu, glucose; F, fructose. Solvent of ethyl acetate, acetic acid and water (9:2:2, v/v). Development with aniline phthalate.

A. Case 6, aged 9 days, diet, breast milk. Samples 1 and 2 are derived from the same stool; sample 2 contained twice as much extract as sample 1. Note:

Fecal sugar consists mainly of galactose and glucose. Above moderate lactose spot there are at least 2 unidentified compounds.

B. Case 6, aged 2 months; diet, soy flour formula. Samples 1, 2 and 3 are derived from stools following GTT and samples 4, 5 and 6 from stools following galactose TT. Note: The glucose spot of sample 6 is obviously from sucrose and glucose in the diet given before and after the test (see also Fig. 5).

other carbohydrate mixtures than glucose and fructose. A typical experiment is portrayed graphically in Fig. 5. The data from this and from similar studies in Cases 1 and 4 are presented in Table 7. The degree of hydrolysis in the upper jejunum was about 25 % for lactose and about 30 % for sucrose and maltose. The luminal concentrations of glucose were higher than those of fructose when sucrose was given in the test meal, indicating that the absorption of glucose was slower than that of fructose (Table 7 Case 4 last experiment).

On several occasions it was found that the fasting patient with GGM had measurable

amounts of glucose in the first specimens of intestinal juice before the test meal had reached the level of intubation. In Case 1 when a test meal without carbohydrate was given, the contents of the jejunum also contained significant amounts of glucose (13 mg/100 ml). When a new test meal containing 3.5 per cent fructose was given, slightly higher values of glucose (maximum 35 mg/100 ml) resulted. During this study the blood glucose varied between 72 and 85 mg/100 ml. In Case 4 before the administration of the xylose-fructose mixture, the fasting glucose concentration of the intestinal juice was 19 mg/100 ml. There

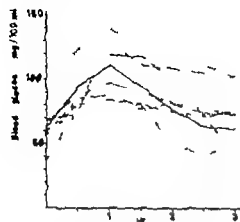


Fig 2 Oral fructose tolerance tests in 5 patients with glucose-galactose malabsorption.

Symbols: — Case 1 Case 3 - - - - Case 4 - . - - Case 5 Note: The increase of blood glucose within the first hour varies considerably (between 7 and 81 mg/100 ml) but usually it exceeds 20 mg/100 ml.

GTT a higher glucose value in the feces was observed, 1.14 % of feces wet weight as compared with 0.07 % at the test, a fact probably due to the diet including a lunch with as a dessert frozen raspberries and sugar. In Case 3 (examined in adulthood) it was considered useless to look for fecal sugars after the oral tolerance tests, since diarrhoea did not result.

Intubation studies These studies were performed in Cases 1, 3 and 4 after intubation of the upper jejunum. Comparison of the glucose and fructose absorption after administration of a test meal containing both of these sugars in equal concentrations was found to be of great value for the diagnosis of GGM: glucose was always absorbed more slowly than fructose (28, 29). In Cases 1 and 4 intubation studies were also performed with test meals containing

Table 5 Xylose absorption tests in two infants with glucose-galactose malabsorption

Test dose: 15 g/sq.m. body surface

Case nr	Age (months)	Blood xylose mg/100 ml		Urinary xylose μ of dose excreted in 8 hours
		30 min	60 min	
5	1	9	15	5
6	13	15	25	9

Table 6. Per cent excretion of sugar in feces within 48 hours after oral administration of different sugars (2 g/kg body wt) together with PEG

Subject	Age	Sugar tested	Recovery (% of test dose)	
			Sugar	PEG
Case 5	1 mo	Glucose	39	—
		Galactose	83	76
		Fructose	14	58
Case 6	2 mos	Glucose	22	74
		Fructose	0.7	94
		Galactose	53	83
Case 6	5 mos	Glucose	39	84
		Galactose	60	96
		Fructose	0.3	70
		Lactose	10 ^a	48
Case 4	4 mos	Lactose	13.5 ^b	—
	6 mos	Fructose	1.9	—
Case 1	3 1/2 ys	Glucose	0.7	66
		Lactose	< 8.5	96
		Fructose	0.4	116

^a Sum of lactose, glucose and galactose measured with specific enzymatic methods. (1.5% of the test dose was recovered as the unsplit disaccharide, the rest of the fecal sugar was 1/3 glucose and 2/3 galactose.)

^b Sum of lactose, glucose and galactose. Lactose and galactose were measured as excess of sugar found by a reduction method after determination of glucose and fructose with specific methods.

As a, but anthrone method for total sugar

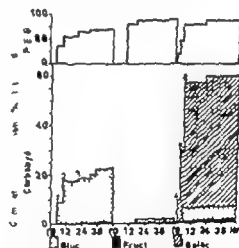


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scribed by Anderson *et al.* (3) died at 3 months, whilst under medical treatment, in a state of emaciation and dehydration. Several relatives to the 6 cases presented here died at 1-3 months of age, probably due to GGM (*cf.* p. 21).

Diagnosis of glucose-galactose malabsorption. The summary of symptoms presented according to these case histories cannot be regarded as entirely pathognomonic for GGM. Almost the same symptoms are seen in congenital lactase deficiency but the combination of glucose in the watery feces and of a slight glucosuria despite low blood sugar levels is highly suggestive towards the diagnosis of GGM. The condition can also be confused with the recently described transient malabsorption of monosaccharides (8), which seems to have an infectious etiology. The results of the sugar loading tests and of the dietetic trial with a formula, in which fructose is the only carbohydrate, show that during the first months of life a guaranteed diagnosis can be made without further investigations. However sugar determinations on the stools passed after the oral sugar loads should not be neglected. In Case 1 (3 1/2 years of age) and Case 3 (adult) no sugar diarrhoea was observed after the sugar TT's. Hence, in patients out of infancy it may be necessary to perform an intubation study with measurement of the relative absorption coefficients of glucose and fructose, in order to obtain a reliable diagnosis.

Some laboratory tests carried out in order to exclude other diarrhoeal conditions may give confusing results. A moderate steatorrhea is sometimes found, as observed in Case 1 and in patients reported by others (3-25). This probably results from a short intestinal passage time. Steatorrhea has also been observed in patients with lactase deficiency (24). Laplane *et al.* (25) reported that, when giving 25 g of glucose in addition to a barium meal, a "détaille péritablique" occurred after a short latent period and at fluoroscopy the barium was then seen to have reached the rectum immediately. The same phenomenon has been ob-

served in patients with lactase (or sucrase) deficiency after the addition of lactose (or sucrose) to a barium meal (27).

Although the histological appearance of the mucosa is normal in GGM (3-37-48) low or borderline values for xylose absorption have been observed in Cases 5 and 6 as well as in other cases of GGM in the literature (1-3-25). This finding could be taken as a sign of general malabsorption. Realizing that under normal conditions xylose is partly absorbed by the active sugar transport mechanism (7-47) the low xylose absorption in patients with GGM may however be explained without the assumption of an unspecific damage to the intestinal mucosa. The active transport mechanism accounting for the major part of the transport of certain sugars, carries only a minor part of the xylose transport. It has been claimed that the major part passes between the epithelial cells (52).

Cause of hyperosmolarity. As judged from the serum electrolyte values (Table 2) the patients suffered from hyperosmolar dehydration when the diarrhoea was at its worst. In adult patients with lactase deficiency it has been shown that, during perfusion of a 1 meter long section of jejunum with a slightly hypotonic solution containing 9% lactose, a net flux of water occurs into the intestinal lumen (23). This is in contrast with the finding in normal subjects when lactose perfusion causes net absorption of water. In a recent study (26) in infants with congenital lactase deficiency it was found that infusion into the stomach of a solution containing 5.4% lactose resulted in a net secretion of water over the whole length of the small intestine. The simultaneous loss of sodium from the blood into the small intestine was comparatively small, and moreover, the colon seemed to reabsorb sodium more effectively than water. Similarly when, in patients with GGM, the lactose of breast milk (lactose content 7%) is gradually hydrolysed by the mucosal lactase, and the absorption of the resulting monosaccharides, glucose and galactose, is very slow the intesti-

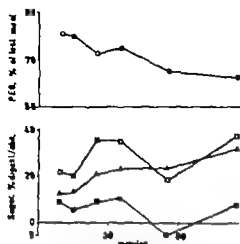


Fig 5 Percentage digestion and absorption of sugars in the upper jejunum (2nd loop) after administration of a test meal containing 2 per cent fructose, 2 per cent maltose and 1 per cent PEG Case 4 aged 7 months. Symbols: \circ PEG \square maltose (% digested); Δ , fructose (% absorbed) \blacksquare , glucose (% absorbed). Note Maltose was hydrolyzed to 20–40 per cent. Less than half of the released glucose was absorbed at this level of the intestine (see also Table 7).

was a small increase in the glucose concentration during the rest of the study with a maximum value of 40 mg/100 ml, but as in Case 1

this increase could at least partly be ascribed to traces of glucose present in the fructose.

Fecal fat determinations Fecal fat has been measured in Cases 1 and 4. When these patients received a soy flour formula steatorrhea was absent. When fed breast milk Case 1 was found to have an average excretion of 15.4 g fecal fat per day.

DISCUSSION

Delineation of the disorder

Natural history of glucose-galactose malabsorption. The typical course of untreated GGM is illustrated by Case 2, who died at an age of about 7 weeks, shortly after admission to the hospital. Her clinical picture resembled that of the other cases, and being a sister of Case 1 there is little doubt regarding the diagnosis. Probably she would have died earlier if breast feeding had been continued for longer than two weeks after birth. A sibling of a case described by Lapiano *et al* (25) died as early as at the age of 8 days. A brother of the patient de

Table 7 Percentage digestion and absorption of sugars in upper jejunum after administration of test meals as observed in intubation studies

The values given are averages from 5–8 samples collected for 90 minutes. Case 1 aged 3 years and Case 4 7 months.

Case no.	Intubation site	PEG (% of test meal)	Sugars in test meal	% digestion	% absorption
1	1st jej. loop	56	Fructose 2	—	32
			Glucose 2	—	6
1	1st jej. loop	38	Fructose 2	—	43
			Lactose 2	22	(glu) 3 ^a
4 ^b	2nd jej. loop	50	Fructose 2	—	31
			Glucose 2	—	18
4	2nd jej. loop	74	Fructose 2	—	20
			Maltose 2	31	7
4	2nd jej. loop	59	Fructose 2	—	22
			Glucose 1	—	9
			Galactose 1	—	—
4	2nd jej. loop	67	Fructose 2	—	33
			Lactose 2	26	(glu) 3 ^a
4	2nd jej. loop	54	Xylose 2	—	17
			Fructose 2	—	33
			Xylose 2	—	12
4	2nd jej. loop	54	Sucrose 2	29	(fru) 11 (glu) 7

^a Galactose absorption was not evaluated.

^b The first intubation study of Case 4 was done 4 weeks before the other studies, which were performed during the course of 4 days with the tube remaining in position.

only small amounts of starch, milk and sugar. Therefore, some discomforts such as abdominal cramps, flatulence and occasional loose stools have to be accepted.

Pathophysiological considerations

As could be anticipated from the dietetic trials where limited amounts of approximately half isotonic glucose solutions did not increase the diarrhoea, the biochemical investigations revealed that there is some absorption of glucose. The GTT's of Fig. 1 invariably show a small increase in the blood sugar at 1 hour. The intubation studies (Table 7) gave further evidence towards this conclusion. The larger amount of galactose recovered from the faeces compared with that of glucose after loading with the respective sugars indicates that galactose is absorbed even more slowly than glucose. The level of blood galactose at the galactose TT's (Table 4) does not significantly differ from zero. As most of the sugar recovered from the faeces appeared within the first 6 hours after the oral loading, it is not likely that a different metabolism by the bacterial flora accounts for the difference in the excretion of glucose and galactose. It has been shown in congenital sucrase deficiency that, when after an oral test dose of sucrose the concentration of sugar in the stools is at maximum (i.e. within 6 hours) there is still comparably little lactic acid, the main bacterial metabolite of unabsorbed sugar (44). Our results are at variance with those of Anderson *et al.* (3) who found less galactose (37% of the dose) than glucose (59% of the dose) in the stools after similar tolerance tests in one patient with GGM. However they collected the stools for only a 6 hour period and did not test the reliability of collection by e.g. using an unabsorbable marker. Using ^{14}C -labelled glucose and galactose, Lineweaver *et al.* (33) found in a case of GGM a higher radioactivity in serum after the administration of glucose than after administration of galactose. The absorption of glucose was calculated to be nearly twice that

of galactose, but this difference was not commented upon.

Under normal conditions galactose is, in man as well as in many other species, absorbed somewhat faster than glucose when these sugars are given separately (4, 19). In the patients with GGM the observed concentration of glucose in the fasting intestinal content, and when sugars other than glucose were administered, was not high enough to assume influence of a competitive inhibition of galactose absorption. The residual absorption of glucose, found to be better than that of galactose, cannot be explained by simple diffusion or reduced rate of transport by the mechanism normally responsible for the bulk of the transport of these hexoses. In patients with GGM, at least part of the glucose seems to be absorbed by a second specific pathway for glucose having a much lower affinity for galactose. This proposed second pathway for glucose absorption has already been speculated upon because of irregularities in the mutual inhibition of the intestinal transport of glucose and galactose (39). If it exists, this second pathway resembles the tubular reabsorption process for glucose, which also has a higher affinity for glucose than for galactose (49).

The concentration of glucose found in the fasting intestinal lumen (13 and 19 mg/100 ml, respectively in the two patients in which this was measured) was below the blood sugar concentration. This does not imply that active absorption still occurs. If merely small amounts of glucose are exchanged between the epithelial cells and the luminal content, the rather low intestinal glucose concentration could be due to dilution by secretions, provided that there are practically glucose-free.

In the adult jejunum, the hydrolysis of sucrose is, under normal conditions, not rate-limiting for the absorption of this sugar (14). There is no reason to believe that the interrelationship between sucrose hydrolysis and subsequent monosaccharide absorption is different in children. During sucrose absorption the intraluminal concentration of monosac-

nal wall will secrete water into the lumen to maintain isotonicity. Disregarding the electrolytes and other solutes in the intestinal juice, the mixture of glucose and galactose must be diluted to 5.5 per cent to be isotonic. By this mechanism the body will lose large amounts of water without a proportional loss of electrolytes. The same situation arises when the patients consume starch, which is gradually converted to glucose. It is thus quite natural that the babies receiving large amounts of carbohydrates such as lactose and starch become very thirsty. As extra water was not given, hyperosmolarity resulted. The renal tubular concentration mechanism, presumably working at maximal capacity is apparently insufficient to compensate for the hyperosmolarity.

Additional disorders The necessity to produce maximally concentrated urine during long periods is a possible explanation for the nephrocalcinosis found at autopsy in Case 2 and for the development of stones in the urinary tract of Case 1 at an unusually early age. In Case 3 the same mechanism may have been responsible.

Case 5 was born at a time when GGM was a well defined entity and it was therefore diagnosed at an early age and successfully treated. His death at 4 months seems to be related to an agammaglobulinaemia. Unfortunately no diagnosis of the type could be made since he died soon after the second admission. The agammaglobulinaemia, however was probably coincidental and unrelated to the disturbed absorption of glucose and galactose.

In the history of Case 6 there were also several complications, including an infantile myocarditis which could not be ascribed to the congenitally disturbed carbohydrate absorption or to secondary malnutrition of important nutritive factors. The initial dietary trials were, it is true, not quite adequate but vitamins, salts and trace minerals were added in sufficient amounts.

Treatment and prognosis Case 3 the adult woman, is probably unique, as she survived before the era of parenteral fluid therapy. For her

it was advantageous that her mother's lactation ceased early and that she was then given a very unorthodox feeding with a low carbohydrate content. Case 1, 4 and 5 were also given diets with a low carbohydrate content (Mullisoy) before the diagnosis was established. The amelioration of the diarrhoea observed when feeding this diet is not only due to a low carbohydrate content but also to the fact that the main carbohydrate component is sucrose. After splitting by intestinal invertase the fructose part of sucrose is well absorbed. However the best therapeutic response in babies was achieved by feeding a formula containing fructose (4-8 per cent) as the only carbohydrate ingredient, this being the logical consequence of the experimental findings. In one patient (Case 6) the therapeutic trial with fructose was misleading; although the diarrhoea improved the patient started to vomit. This cannot be readily explained, but the rather high casein content of the formula may have played a role. Later the formula was well tolerated.

The reduction of clinical symptoms after oral sugar tolerance tests parallels the increased tolerance to dietary carbohydrates with increasing age. The experimental data of the present and previous studies (29-37) gave no evidence of a more rapid absorption with increasing age. The adaptation is therefore illusory and is probably the result of a combination of factors. (1) the size of the intestinal tract increases more than the caloric needs and the intake of carbohydrates. (2) due to a longer intestinal passage time beyond infancy a larger part of a test dose can be absorbed, and (3) the bacterial flora has more time to metabolize the sugar. Furthermore, because of the consumption of a diet containing badly absorbed carbohydrates, the older patients may have developed a larger saccharolytic bacterial flora.

If recognized in time, GGM has a favourable prognosis with correct dietetic measures the development of the children both physically as well as mentally is normal. As the patient grows up it becomes increasingly impractical to adhere to a strict diet containing

GLUCOSE-CALACTOSE MALABSORPTION

A Genetic Study

K. MELIN and G. W. MEEUWISSE

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Glucose-galactose malabsorption (GGM) is, as described in the previous pages, a congenital disorder characterized by watery acid mel-stoolbes from birth. Practically all the reported cases of GGM have a mild glucosuria, that of Dobols *et al.* (12) is an exception.

In a preliminary report we mentioned 3 related, female cases of GGM where the parents were all mutually related (31). GGM was concluded to be a recessively inherited disorder. In a later communication a male case was reported (32). The present article contains a detailed pedigree. In order to find a method of detecting heterozygotes, biochemical investigations on carbohydrate metabolism were undertaken on parents of some of the patients with GGM. The pattern of amino acid excretion by the kidney was studied in five of the patients and their parents.

MATERIAL AND METHODS

The patients, coded 1-6 (Fig. 1), were presented with their case histories in the previous pages. Cases 2 and 5 died in the hospital at the age of 3 and 4 months, respectively. Cases 1, 4 and 6 are children, aged 10, 7 and 6 years, respectively. Case 3 is now a woman of 42.

Abbreviations: β -ATB, β -amino isobutyric acid; GGM, glucose-galactose malabsorption; GTT, glucose tolerance test.

The pedigree has been made up from data gathered through numerous interviews among relatives of the patients and from parish registers, of which photocopies are available at the city library of Umeå. The ancestors on the top of Fig. 1 were found by tracing back from Case 1 and 2. Other probands were Case 4 and Case 6. Except in the last 3 generations no thorough efforts were made to trace the offspring of siblings of the ancestors (in our probands in order to find further cases of GGM).

Qualitative estimation of urinary glucose was done with Clinohelz strips. The glucose tolerance of the parents of some patients was tested with oral doses of 50 g glucose. Blood glucose was measured by glucose oxidase method (10). The excretion of amino acids in the urine was estimated quantitatively by the ninhydrin method. The pattern of amino acid excretion was studied by two-dimensional paper chromatography. The necessary 24-hour specimens of urine were obtained while the patients were under treatment and in a good nutritional state.

RESULTS

Genealogy

The pedigree of the patients with GGM (Fig. 1) has black symbols for known, diagnosed cases. Probable cases (hearsay evidence) have been represented by hatched symbols. The numerous intermarriages in the middle of the chart were brought about by the geographic isolation of the area in which these people were living. The patients, as well as the common ancestors to whom all the patients could be traced, belong to the white, European race;

charides is small and fructose is present in a higher concentration than glucose (14). In GGM the decreased absorption of glucose after sucrose hydrolysis (Table 7 Case 4) results in a higher intraluminal concentration of glucose than of fructose. The fact that in no experiment with a disaccharide does the absorption of glucose exceed $1/2$ of the amount released by hydrolysis (Table 7) contrasts also with the results obtained in perfusion studies on normal individuals. In the latter the main part of released glucose never appears in the lumen (15).

In a previous article (28) it was reported that patients with GGM are capable of splitting ingested disaccharides into monosaccharides. The findings in the stools of small amounts of disaccharide after lactose ingestion (Case 6) and after sucrose ingestion, as observed by Laplane *et al* (25) in one of their patients, indicate, however that disaccharide hydrolysis in patients with glucose-galactose malabsorption is not always complete. There is no deficient activity of disaccharidases in mucosal specimens from patients with GGM (1, 3, 37). Probably the most important factor allowing unsplit disaccharide to appear in the stools is the short intestinal passage time after administration of badly tolerated carbohydrates.

The intubation studies showed that glucose and galactose released from the disaccharides by the mucosal disaccharidases are given no opportunity to by-pass the defective transport mechanism. Hence, if the "metabolic block" is located at the entry step of the monosaccharides into epithelial cells, the most plausible location of the defect with regard to current concepts (37) the disaccharidases seem to exert their effect before complete penetration of the sugar through the cell membrane.

SUMMARY

The histories of 6 cases, 2 male and 4 female, with glucose-galactose malabsorption (GGM) are presented. Of these, 4 have survived and are in good general health on a diet with a reduced carbohydrate content. One case died at 2 months of age with severe malnutrition

due to intractable diarrhoea before a diagnosis was made. The other patient who died, was diagnosed and treated from the neonatal period, and he was progressing until infection occurred by a *Candida albicans* followed by death at 3 months of age in a picture of agammaglobulinaemia. One patient is now a woman of 41. The main symptoms are diarrhoea from birth, dehydration and malnutrition. Glucose is found in the watery stools and there is also a slight glucosuria. Hyperosmolar serum is often seen. Two patients, not those treated at an early stage, developed renal concretions probably owing to the long lasting water loss with the stools. Treatment during the first months consisted of replacement of the ordinary dietary carbohydrates by fructose. Although the basic biochemical disorder lasts throughout life, limited amounts of starch and milk could be introduced later in infancy. Some absorption of glucose could be demonstrated, tentatively due to a second pathway for intestinal glucose absorption which is apparently not shared by galactose. Hydrolysis of disaccharides occurred in the small intestine of GGM patients but the released glucose was absorbed no better than when administered as a monosaccharide. This implies that the site of disaccharidase activity is located more superficially at the luminal side of the epithelial cell membrane than the disturbed step of glucose and galactose transport.

ACKNOWLEDGEMENTS

From the cottage hospital of Stensåle, Dr A. Frykholm referred Case 1 and Dr T. Sæve referred Case 2. Case 4 was referred by Dr P. G. Bergfors, Skellefteå. The post mortem examination of Case 2 was performed by Dr B. Larsson and Professor C.-M. Fajera, Umeå, and of Case 5 by Professor S. Falkmer and Dr L. Hassler, Umeå. The histology of lymphoid tissues and the lungs of Case 5 were also examined by Dr G. Nathorst Windahl, Uppsala. The authors are grateful to all these colleagues.

This work was supported by grants from the University of Umeå, the University of Lund, the Swedish Medical Research Council and the Swedish Nutrition Foundation.

Key words: Malabsorption, glucose, galactose, disaccharides, absorption tests, diet, hyperosmolar dehydration.

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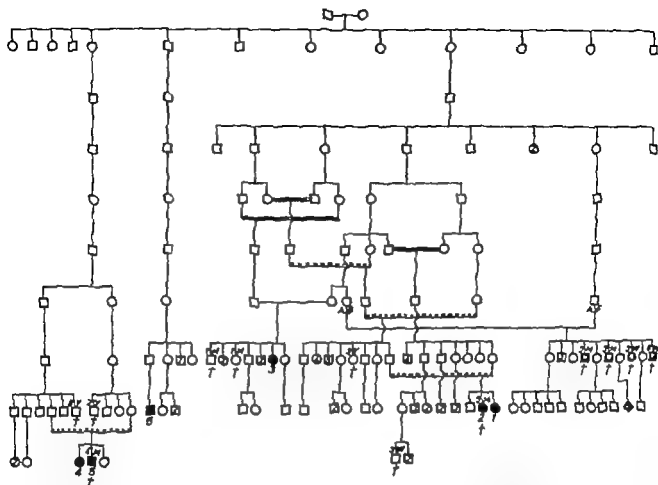


Fig 1 Pedigree of the six patients with glucose galactose malabsorption. All could be traced back to one sibship, born in the beginning of the 18th century. The numbers below the filled symbols correspond with those of the case histories. Age at death of some individuals is indicated above their respective

symbols. Numbers within symbols refer to the number of consecutive sibs of the same sex or unspecified sex (diamond). Symbols: ■, affected males; ●, affected females; ◐, probable affected relatives with early death; — marriage between cousins, — marriage between second cousins.

they are not Lapps.¹ The couple of common ancestors gave birth to 13 children in the beginning of the 18th century.

Cases 1 and 2 are 3rd and 2nd children to parents who were second cousins in two ways. The father had a sister who was dwarfed and mentally retarded. She died at the age of 3 but there was no history of diarrhoea. The parents of Case 3 were third cousins. In this family there were eight more children, two of whom died at about 1 month of age from pneumonia.

They had no diarrhoea. The parents of Cases 4 and 5 are second cousins. A healthy 3rd child has recently been born to them. Both parents had a brother who died at a young age, without having suffered from diarrhoea. The father but not the mother of Case 6 could be proved to be a distant relative of the other patients with GGM. The mother's pedigree could not be completed beyond 5 generations.

In the last generation on the pedigree chart (Fig. 1) there is one boy who died at a cottage hospital from severe diarrhoea at 3 weeks of age. His maternal grandfather is a brother of the mother of Cases 1 and 2. The pedigree of the father of this infant has not been ascertained. The boy was born at term in a breech

In ancient times the north of Sweden was inhabited only by Lapps, a numerically small race with traits differing from the rest of the Swedish people. Sweden of other origin began to colonize the area in the 16th century.

delivery. At birth he was small for date and asphyctic, but for the first two weeks his condition was reasonably good, and breast-fed his weight increased from 1810 g to 2110 g. Vomiting and watery diarrhoea started when a cow's milk formula was introduced and this condition lasted one week until his sudden death. As the history during the first two weeks speaks against GGM, he is not regarded as a probable case of this disorder. An aunt (A.G. in Fig. 1) of Case 3 married to a distant relative (A.F.), had 12 children, 4 of them died between the age of 3 weeks and 3 months from intractable diarrhoea commencing in the newborn period. They were all breast-fed. The mother of Case 3 had helped her sister to nurse these children, and she stated that the symptoms were identical to those of her own daughter. Moreover the annotations in the parish registers were compatible with the diagnosis of GGM in 3 of these infants. In the 4th case there was no mention of the cause of death. According to information from relatives there were 2 more children in this family twin, who died in the same picture of watery diarrhoea at a few weeks of age. They however were not recorded in the parish registers.

Biochemical investigations

The parents of Cases 1 and 2, of Cases 4 and 5 and of Case 6, were repeatedly tested for glucosuria. Glucosuria after meals was found on two occasions only in the father of Cases 1 and 2. During an oral glucose tolerance test, when the blood glucose rose from 89 to 147 mg/100 ml in 30 minutes, no glucosuria occurred. The mother of these two girls and the parents of Case 4 had normal GTT's too. The other parents were not studied with a GTT.

Examination of the urinary excretion of amino acids revealed that Cases 1, 3, 4 and 6 but not Case 5 excreted increased amounts of β -aminobutyric acid (β AIB). The total excretion of α -amino acids was normal. Amongst the parents, the father of Cases 4 and 5 and the mother of Case 6 excreted increased amounts of β AIB. The other parents excreted

normal or undetectable amounts of this compound. β AIB excretion could not be investigated in the father of Case 3.

DISCUSSION

Five of the cases of GGM, represented by a solid symbol in Fig. 1 belong to 3 sibships with a total of 15 children. In all these cases the parents were related to one another. The sixth case of verified GGM is the only child of his parents. An ancestral relationship between these parents could not be proved. The father however is a descendent of the large family from which all other patients originate.

From the pedigree, containing both male and female cases, and from the fact that the parents are healthy with no history of chronic diarrhoea in childhood, it can be concluded that the disorder has an autosomal, recessive mode of inheritance. The literature is not at variance with this concept. The parents in the case presented by Nusslé and Gautier (40) are first cousins.

Laplane *et al.* (25) described two unrelated boys with GGM. A brother of one of them died from a disease with similar symptoms at 8 days of life, whilst a sister was healthy. The other case had two healthy brothers. Anderson *et al.* (3) described a girl with GGM. Her brother died at 3 months of age in the same clinical picture. Single cases have been reported by several authors (1, 12, 21, 33-35, 40, 48). Some of these patients have healthy siblings.

Milk intolerance due to acquired lactase deficiency was found in the father of the case of Abraham *et al.* (1). It was considered incidental. The father of Nusslé's and Gautier's case had a history of chronic diarrhoea in childhood, but was found to be normal in adulthood. Symptoms suggestive of sugar malabsorption have not been present in the parents of other cases in the literature.

All published cases of the disorder have either been white ("Caucasian") or of unmentioned origin with one exception: the

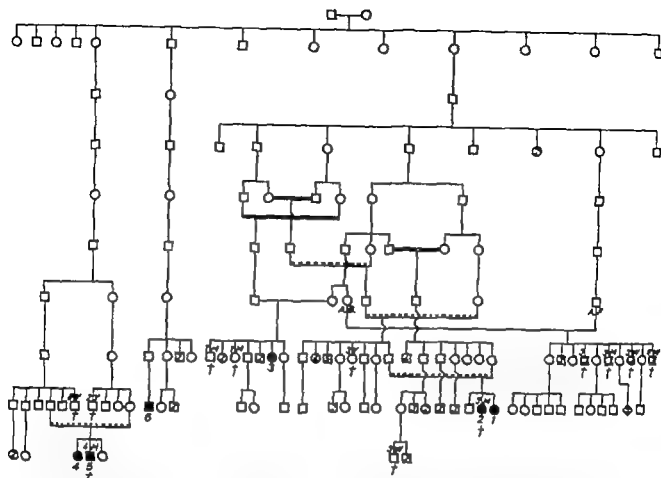


Fig 1 Pedigree of the six patients with glucose-galactose malabsorption. All could be traced back to one sibship, born in the beginning of the 18th century. The numbers below the filled symbols correspond with those of the case histories. Age at death of some individuals is indicated above their respec-

tive symbols. Numbers within symbols refer to the number of consecutive sibs of the same sex or unspecified sex (diamond). Symbols: ■, affected male; ●, affected female; ◐, probable affected relatives with early death, ΔΔ marriage between first cousins, ΔΔΔ marriage between second cousins.

they are not Lapps.¹ The couple of common ancestors gave birth to 13 children in the beginning of the 18th century.

Cases 1 and 2 are 3rd and 2nd children to parents who were second cousins in two ways. The father had a sister who was dwarfed and mentally retarded. She died at the age of 3 but there was no history of diarrhoea. The parents of Case 3 were third cousins. In this family there were eight more children, two of whom died at about 1 month of age from pneumonia.

They had no diarrhoea. The parents of Cases 4 and 5 are second cousins. A healthy 3rd child has recently been born to them. Both parents had a brother who died at a young age, without having suffered from diarrhoea. The father but not the mother of Case 6 could be proved to be a distant relative of the other patients with GGM. The mother's pedigree could not be completed beyond 5 generations.

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All published cases of the disorder have either been white ("Caucasian") or of unmentioned origin with one exception: the

father of the patient of Abraham *et al.* (1) was Chinese whilst the mother was Irish.

Including siblings who were at death not diagnosed as cases of GGM but who apparently suffered from this disease, the number of reported patients with GGM now amounts to 20. This relatively low figure, despite the fact that the disorder has been recognized for 6 years (25-28) indicates that the gene frequency is rather low. The pedigree of our patients also speaks in favour of a low gene frequency: in only one case (Case 6) consanguinity could not be demonstrated, and this may be due to the fact that the pedigree of the mother became incomplete when traced back for more than a few generations. To our knowledge, only one more case of GGM has been diagnosed in Sweden in a different part of the country (21). A possible relationship with the patients of the family reported here has not yet been sufficiently investigated.

As mentioned in the beginning of this article, glucosuria seems to be a constant finding in the patients with GGM. As the glucosuria is slight, it has to be repeatedly looked for especially if only moderately sensitive methods like Clinistix® are used. The parents who were examined disclosed no glucosuria except for one father where the occasional glucosuria seemed to have a pre-renal cause. GTT's performed on two couples of parents were normal. Hence, it was not possible to demonstrate carriers of the recessive gene by these methods. Incubation studies performed with biopsy specimens from the proximal jejunum of the parents of a child with GGM gave no evidence of reduced active transport of glucose into the mucosa of heterozygotes (37).

In order to investigate whether the patients with GGM have signs of tubular malfunction other than glucosuria, the urinary excretion of amino acids was studied. Although considerable confusion exists as to the causes of increased excretion of β AIB it can be said that it is probably not due to a decreased tubular reabsorption (5). Between 5 and 10 per cent of healthy adult Occidentals seem to have an

increased excretion of β AIB as a recessively inherited trait (7-17). Among Orientals the percentage of "excretors" is about 25 per cent (5-7). The frequency of excretors in Occidentals has later been questioned (3). In children a large excretion of β AIB is fairly common. It has been found in connection with a variety of disorders, e.g. iron or iron-copper deficiency anaemia (7). Too little is known about the metabolic sources of this β amino acid for any conclusions to be drawn. Among other influences, nutritional factors are probably involved in nongenetic excretors (7). Mild liver disease has also been mentioned as a cause (5). Our patients showed no anaemia, no signs of malnutrition or liver malfunction when their excretion of amino acids was examined. An altered carbohydrate metabolism due to a subnormally low exogenous glucose supply and appreciable amounts of dietary fructose might have influenced this to some degree. With regard to the unspecificity of the increased β AIB excretion in children there is at present little reason to believe that four of our patients happened to belong to the group of genetical β AIB excretors. On the other hand no evidence can be put forward regarding any relation between the high excretion of β AIB and the disturbed transport of sugar in GGM.

SUMMARY

The pedigree of 6 cases (2 male and 4 female) of glucose-galactose malabsorption is presented. Besides the 6 cases seen by the authors, there occurred in the same pedigree at least 4 more instances of death in early infancy due to intractable diarrhoea. It is likely that these resulted from glucose-galactose malabsorption. The parents of the patients were healthy and had no history of chronic diarrhoea in infancy or thereafter. As judged by oral GTT's on two pairs of parents they had normal glucose absorption. No renal glucosuria, present in all the patients, was found in the parents. It was concluded that glucose-galactose malabsorption

has an autosomal recessive mode of inherit-
ance.

In 5 patients (from 4 different sibships)
where the urinary excretion of amino acids was
examined, 4 had increased excretion of β -
aminoisobutyric acid although they were in a
good nutritional state. Of 7 parents examined,
2 excreted increased amounts of the same com-
pound. The finding of this selective amino-
aciduria is probably incidental and, at least in
the children, is not believed to be genetically
determined.

ACKNOWLEDGEMENTS

The authors received the kind help of Dr R. Jagne-
berg (Dep. of Clinical Chemistry Sahlgrenska Spital,
Göteborg) and had the advantage of his vast
experience in evaluating the excretion of amino acids.
Among the many helpful people giving valuable in-
formation on the pedigree, Mrs Jenny Arkblad, Berg-
löva, has to be mentioned with gratitude. Part of the
genologic study of Case 6 was done by Mr K. Lund-
berg, Stockholm.

This investigation was supported by grants from
the University of Umeå, the county authority (Väster-
botten län landsting) and the Swedish Nutrition
Foundation.

Key words: Malabsorption, glucose, galactose, renal
glucosuria, β -aminoisobutyric acid excretion, hered-
ity

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